

Metabolic effects of antipsychotic treatment in children with mental health conditions

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- Consultant fees from Eli Lilly Canada Inc. (unrelated to this presentation)



Objectives

1. Briefly describe the epidemiology of second-generation antipsychotic (SGA) prescribing practices in North America
2. Summarize the literature on the metabolic effects of SGAs
3. Describe a multi-disciplinary approach including evidence-based guidelines and resources for monitoring and management of these metabolic complications



A patient encounter sparked my curiosity...

In 2006, called from a pediatrician in Prince George about

- 14 yo boy who developed diabetic ketoacidosis; notably, he had been started on Quetiapine the week prior; required treatment with insulin for several weeks;
- Quetiapine weaned after a few months and he came off insulin
- Had I seen this before?
- Subsequently, ran into one of the psychiatrists in the ER;
– she had observed that some kids had come back a year later after starting one of these meds having put on 50 pounds!



A couple of other cases... Case 1

- 17 year old boy
- Dx: Schizoaffective Disorder (dx at age 12) and Asperger Syndrome (Autism Spectrum Disorder)
- 28 lb weight gain since starting Clozapine (3 months ago) [prev failed olanzapine and risperidone]
- Anthropometrics at 1st visit:
 - weight 121.1 kg (>97%ile);
 - height 177.8 cm (50-75%ile);
 - BMI 38.3 (>97%ile);
 - waist circumference 118 cm (>90%ile)
- Consult Question: ROLE for Metformin?



Case 2...

- 6 year old boy
- Prenatal substance exposure, developmental delay, autistic features, difficulties with behaviour and aggression
- Referred for: Prolactin 175.6 ug/L (N:<20ug/L)
– (Note: no prolactin had been done at baseline)
- Current Medications: Risperidone 1.25 mg PO OD
- No symptoms of hyperprolactinemia
- CONSULT QUESTION: Do we need to do an MRI or can this be blamed on the risperidone alone?

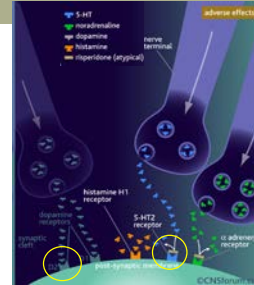


Background

- 15% of youth and 20% of adults in Canada suffer from mental illness
- Many will undergo a combination of non-pharmacologic and pharmacologic interventions
- One pharmacologic intervention is the use of **second generation (atypical) antipsychotics (SGAs)**:
 - Risperidone (Risperdal®)
 - Quetiapine (Seroquel®)
 - Olanzapine (Zyprexa®)
 - Aripiprazole (Abilify®)
 - Ziprasidone (Zeldox®)
 - Clozapine (Clozaril®)
 - Paliperidone (Invega®)

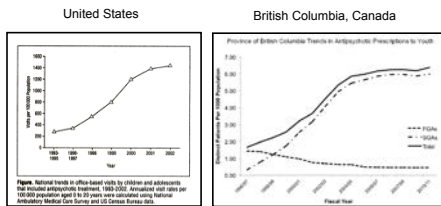


Second-generation Antipsychotics (SGAs)



- D₂ Receptor Blockade**
 - Positive symptoms of psychosis
 - ↓ Extrapyramidal symptoms
- 5-HT₂ Receptor Blockade**
 - Negative symptoms of psychosis
 - Affect Dysregulation
 - ↑ Cognition

Rapid Increase in Antipsychotic Prescriptions to Children and Adolescents



Olsson et al. (2006). Archives of General Psychiatry, 63: 679-685

Ronsley R et al. (2013). Canadian Journal of Psychiatry

For what symptoms and diagnoses are SGAs prescribed in kids in Canada?

Indication	Percentage of prescribers by indication (%)
Tourette syndrome	78.8
Schizophrenia	81.8
Bipolar mood disorder	80.0
Depression	30.0
Tourette syndrome	73.5
Eating disorders	25.0
Obsessive-compulsive disorder	52.3
Posttraumatic stress disorder	33.5
Other anxiety disorders	30.0
Pervasive developmental disorder	80.4
Mental retardation	48.2
Attention-deficit hyperactivity disorder	51.2
Oppositional defiant disorder	51.2
Conduct disorder	50.4
Impulsivity	65.3
Poor frustration tolerance	74.3
Affective dysregulation	84.7
Insomnia	35.9

Doey T et al. Canadian J of Psych (2007) 52: 383-388

RCT-supported evidence for SGA use in kids is LIMITED

- All SGA use in children in Canada is off-label*

Indication	Target Symptoms
Autism [†] and Pervasive Developmental Disorders	Irritability, Aggression
Bipolar I Disorder [†]	Manic or mixed episodes
Conduct Disorder	Aggression
Developmental Disabilities	Aggression, Self-injurious behaviour
Disruptive Behaviour Disorder	Conduct problems, Irritability, Hyperactivity, Aggression
Tourette Syndrome	Tics
Schizophrenia [†]	Positive and negative symptoms

*except for Aripiprazole for youth aged 16-17 with schizophrenia and 13-17 yo with manic/mixed episodes of BP I

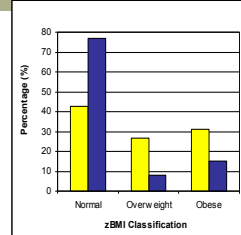
What are the risks associated with second generation antipsychotics?

Metabolic Side Effects - Children

- Up until 2009, studies in kids were limited:
 - Short duration; assessing only absolute weight gain
 - Secondary outcome measures in studies of treatment efficacy
- No guidelines available for metabolic monitoring in children and adolescents



Increased Risk of Overweight/Obesity



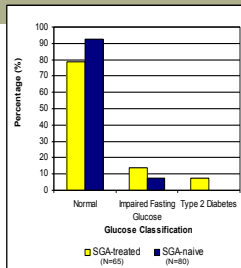
SGA-treated: 57.5%
vs.
SGA-naïve: 23%

P<0.01 by Two-Way Chi Square

Panagiotopoulos et al. (2009). Can J Psychiatry



Increased Risk of Glucose Intolerance



SGA-treated: 21.5%
vs.
SGA-naïve: 7.5%

P=0.014 by Two-Way Chi Square Analysis

Panagiotopoulos et al. (2009). Can J Psychiatry



Cardiometabolic Risk of Second-Generation Antipsychotic Medications During First-Time Use in Children and Adolescents

Online article and related content current as of October 23, 2009.

Christoph U. Correll; Peter Manu; Vladimir Oshansky; et al.
JAMA. 2009;302(16):1755-1773 (doi:10.1001/jama.2009.1549)

Nonrandomized Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) cohort study

- Patients aged 4-19 years with 1 week or less of lifetime antipsychotic treatment
- 272 patients were included in analysis with a mean antipsychotic exposure time of 10.8 weeks



Results: Mean Weight Gain (Kg)

SGA	Weeks 0-4	Weeks 0-8	Weeks 0-12
Olanzapine (N=45)	4.52*	6.68*	8.54*
Quetiapine (N=36)	2.87*	4.85*	6.06*
Risperidone (N=135)	2.72*	4.63*	5.34*
Aripiprazole (N=41)	1.61*	3.34*	4.44*
Untreated (N=15)	1.00	0.78	0.19

*P<0.001

Correll, C. U. et al. JAMA 2009;302:1765-1773.



Results: Increase in Waist Circumference (cm)

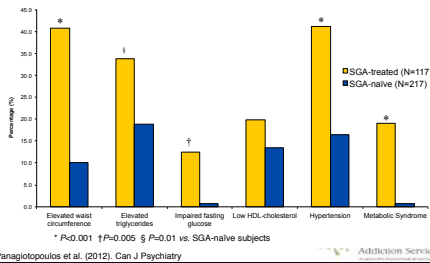
SGA	Weeks 0-4	Weeks 0-8	Weeks 0-12
Olanzapine	4.09*	6.79*	8.55*
Risperidone	2.85*	4.60*	5.10*
Quetiapine	2.74*	4.50*	5.27*
Aripiprazole	2.20*	4.28*	5.40*
Untreated	0.84	0.94	0.70

*P<0.001

Correll, C. U. et al. JAMA 2009;302:1765-1773.



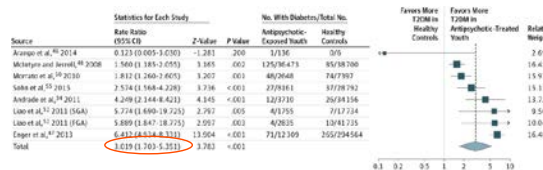
Increased Prevalence of the Metabolic Syndrome and its Components



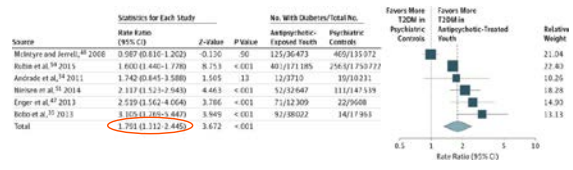
Results: New-onset metabolic complications

Complication	Incidence (%)	
	6 months	12 months
Overweight or obese	34.5	44.8
Waist circumference ≥90 th percentile	22.2	22.2
Fasting glucose ≥5.6 mmol/L	5.9	14.7
Insulin resistance (HOMA-IR >4.4)	3.2	9.7
Hypertriglyceridemia (≥1.24 mmol/L)	25.0	35.7

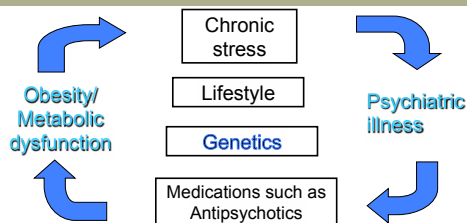
Increased incidence of type 2 diabetes in antipsychotic-treated youth vs. healthy controls



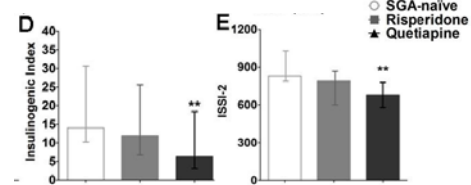
Increased incidence of type 2 diabetes in antipsychotic-treated youth vs. psychiatric controls



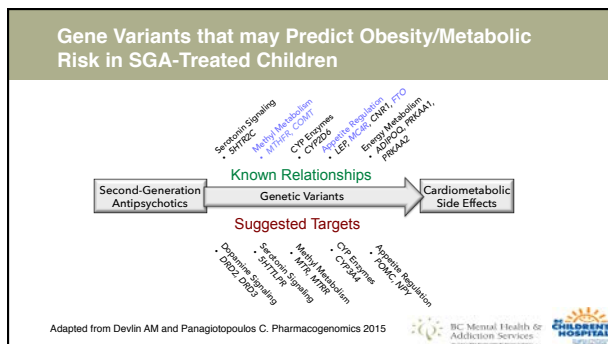
Complex Inter-relationship...



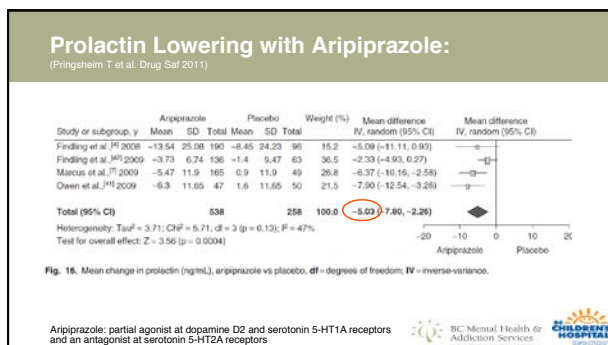
Beta-cell function is impaired in youth treated with SGAs



Y Ngai, P Sabatini, J Davidson, D Nguyen, J Chanoiné, AM Devlin, F Lynn, and C Panagiotopoulos. J Clin Psychopharmacol. 2014.



- ### Prolactin
- All SGAs with exception of aripiprazole cause some degree of prolactin elevation
 - Elevations in prolactin may be associated with
 - Gynecomastia
 - Galactorrhea
 - Infertility
 - Menstrual irregularities
 - Sexual dysfunction, decreased libido
 - Acne and hirsutism (females)
 - Hyperprolactinemia may be asymptomatic in some individuals, particularly pre-pubertal children.



Other Metabolic Concerns

Metabolic Parameter	Clinical Implications
Elevated Liver Enzymes	Non-alcoholic steatohepatitis vs. drug-induced transaminitis
Elevated Amylase	Pancreatitis
Elevated TSH*	Hypothyroidism

*associated with Quetiapine treatment only

- ### Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guidelines - 2011
- Prior to our research, no clinical practice guidelines in children and adolescents for metabolic monitoring
 - ADA/APA had developed adult recommendations since 2004 but poor uptake
 - Evidence-based recommendations on BOTH monitoring and treatment for metabolic complications
 - Writing group included 19 members across Canada with different clinical backgrounds
 - Promotes the use of the Metabolic Assessment, Screening & Monitoring Tool as a practical user-friendly resource

- ### CAMESA Guidelines Process
- No industry sponsorship (CIHR funded)
 - Recommendations created by:
 - Incorporating results of systematic review of the literature on metabolic complications
 - Nominal group process
 - External review by Can Acad Child & Adolesc Psychiatry AND Can Pediatric Society
- The CAMESA guideline group includes:
- Debay Bellemare, Neurologist, University of Montreal
 - Lisa Casselman, Consultant, Mental Health Commission of Canada
 - Jana Davidson, Child Psychiatrist, University of British Columbia
 - Aud Drape, Pediatric Neurologist, University of Ottawa
 - Silvia Orvaschel, Pediatric Nephrologist, University of Calgary
 - Josephine Yu, Pediatric Endocrinologist, University of Calgary
 - Rebecca Joffe, Pharmacist, Alberta Children's Hospital Mental Health Program
 - Carl Mathison, Consultant, Mental Health Commission of Canada
 - Brian McCordie, Pediatric Cardiologist, University of Toronto
 - Jane McLennan, Child Psychiatrist, University of Calgary
 - Yolene Pabst, General Internal and Clinical Epidemiologist, University of Toronto
 - Christoph Pongracz, Pediatric Endocrinologist, University of British Columbia
 - Scott Pillon, Psychiatrist and Clinical Epidemiologist, University of Calgary
 - Michelle Pivonia, Child Psychiatrist, University of Toronto
 - Jennifer Pivonia, Developmental Pediatric Neurologist, University of Ottawa
 - Yolande Prosser, Neurologist and Clinical Epidemiologist, University of Calgary
 - Roger Thomas, Family Physician, University of Calgary
 - Wagner Whitaker, Child Psychiatrist, University of Calgary
 - Chris Wilton, Child Psychiatrist, University of Calgary

Metabolic Assessment, Screening and Monitoring Tool

Metabolic Assessment, Screening and Monitoring Tool

Metabolic Monitoring Tool

CHILDREN'S HOSPITAL

Comparison of Monitoring at BCCH Before and After Protocol Implementation

Metabolic Parameter	Measured (2005-2007) ¹	Measured (2008-2010) ²
Height	39%	89%
Fasting Glucose	34%	74%
Lipids	32%	Cholesterol: 89% Triglycerides: 89%
Blood pressure*	40%	99%

*With height available to assess norms

¹ Panagiotopoulos et al. (2009). Can J Psychiatry
² Panagiotopoulos et al. (2012). Can J Psychiatry

BC Mental Health & Addiction Services
 CHILDREN'S HOSPITAL

Provincial Child and Youth Healthy Living Initiative

- This initiative aims to address healthy living challenges that are prevalent in children and youth with mental health conditions
- Three components:
 - Provincial Mental Health Metabolic Program
 - Kelty Mental Health Resource Centre Website
 - Healthy Living Toolkits for Professionals & Families
 - Additional resources
 - Patient & Family Guide to Second-Generation Antipsychotics
 - Physician Handbook for Metabolic Monitoring
 - Online Metabolic Monitoring Training Module (coming soon)

BC Mental Health & Addiction Services
 CHILDREN'S HOSPITAL

Provincial Mental Health Metabolic Program in BC

<http://www.bcchildrens.ca/health-professionals/clinical-resources/mental-health/metabolic-complications>

- Provides specialized care to children and youth with mental health disorders who are at risk for, or are experiencing obesity and metabolic side effects associated with the use of psychotropics
- The multi-disciplinary team includes a:
 - Pediatric Endocrinologist
 - Nurse Practitioner
 - Dietitian
 - Physiotherapist
 - Child & Adolescent Psychiatrist
- The team provides:
 - Lifestyle counselling: frequent contact/ support
 - Treatment of complications

What is the Provincial Mental Health Metabolic Program?

BC Mental Health & Addiction Services
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Kelty Mental Health Resource Centre Website

<http://keltymentalhealth.ca>

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Healthy Living Toolkits for Professionals and Families*

(*Also available in French, Farsi, Punjabi, Korean, Traditional Chinese, and Simplified Chinese)

- Modules include:
 - Getting Started (a suggested approach to using the toolkit)
 - Healthy eating
 - Physical activity
 - Sleep
 - Stress management
- Sections include:
 - Key Messages
 - Discussing Healthy Living with Children and Youth
 - Addressing Challenges to Healthy Living
 - Medications and their Effects on Healthy Living
 - Resources and Handouts

BC Mental Health & Addiction Services
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Healthy Living Toolkit Instructional Videos

5 videos produced to demonstrate SMART Goal-Setting using the Healthy Living Toolkits

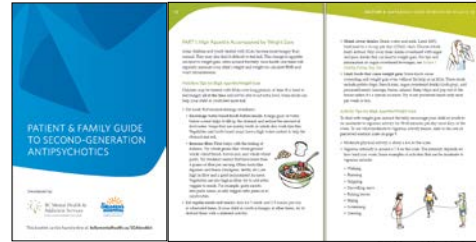
Family Toolkit:
 - Physical Activity
 - Healthy Eating

Professionals Toolkit:
 - Physical Activity
 - Nutrition
 - Sleep

<http://www.youtube.com/watch?v=TVMbQTY4M-4>



Patient & Family Guide to Second-Generation Antipsychotics



Specific Patient Handouts



Case 1...

- 17 year old boy
- Dx: Schizoaffective Disorder (dx at age 12) and Asperger Syndrome (Autism Spectrum Disorder)
- 28 lb weight gain since starting Clozapine (3 months ago) [prev failed olanzapine and risperidone]
- Anthropometrics at 1st visit:
 - weight 121.1 kg (>97thile);
 - height 177.8 cm (50-75thile);
 - BMI 38.3 (>97thile); waist circumference 118 cm (>90thile)
- Consult Question: ROLE for Metformin?



CAMESA Treatment Recommendations: Abnormal BMI or Abnormal WC

1. Overweight (85th ≤ BMI < 95th percentile)
 - Re-evaluate use of SGA (Grade 3)
 - Consider Cognitive/Behavioural lifestyle intervention aimed at weight loss (Grade 1B)
2. Obese (≥ 95th percentile)
 - As per overweight (Grade 3) AND
 - Consider metformin in consultation with specialist (Grade 2B)



Metformin

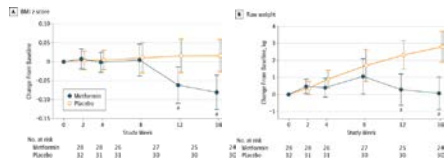
Table 2 Comparison of child and adolescent studies assessing the impact of metformin on weight and glucose-related parameters

Study and ethnicity	Treatment length	Intervention/diagnostic	Nonpharmacological intervention	Outcomes assessed	Significant outcomes at study conclusion
Arvan et al. (2006) Saudi Arabian	12 weeks RCT	49 FEP treatment-naïve patients randomized to either RIS+MET or RIS+PBO	None reported	BW, BM, BSL	NC difference between groups
Klein et al. (2006) USA	16 weeks RCT	18 patients SGA-MET 20 patients SGA-PBO	Nutritional counselling, individualized goals provided for patients	BW, BM, WC BSL, insulin, HOMA-IR	Weight related: Significant 4.08kg reduction in BW 1.12 reduction in BM 4.65cm reduction in WC
Morrison et al. (2002) USA	12 weeks Open label	18 patients SGA-MET	None specified	BW, BM	Weight related: 2.93kg reduction in BW 2.22 reduction in BM

BSL, fasting blood sugar level; BW, body weight; HOMA-IR, homeostasis method of assessment - insulin resistance; MET, metformin; PBO, placebo; RCT, randomized controlled trials; RIS, risperidone; SGA, second generation antipsychotic.



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



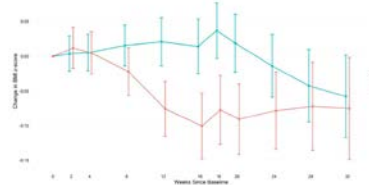
Metformin Effect on Body Mass Index (BMI) z Score and Weight Change Estimates of means for the treatment and placebo groups at each visit. Error bars indicate 95% CIs. * Significant difference at each visit.

JAMA Psychiatry. 2016;73(9):928-937. doi:10.1001/jamapsychiatry.2016.1232



Open-label extension of RCT shows significant lowering of zBMI in those taking placebo with maintenance in those on metformin

FIGURE 1 Change in body mass index (BMI) z score across 32 weeks by group. Note: M-M = metformin to metformin group; P-M = placebo to metformin group.



J Am Acad Child Adolesc Psychiatry 2017



Back to Case 1...

75 gram OGTT:

- Fasting glucose: 6.2 mmol/L
- 2hr glucose: 8.2 mmol/L

Recommendation:

- Start Metformin at 500 mg PO at dinner and increase by 500 mg increments to a final dose of 1000 mg PO BID



Case 2...

- 6 year old boy
- Prenatal substance exposure, developmental delay, autistic features, difficulties with behaviour and aggression
- Referred for: Prolactin 175.6 ug/L (N:<20ug/L)
 - (Note: no prolactin had been done at baseline)
- Current Medications: Risperidone 1.25 mg PO OD
- No symptoms of hyperprolactinemia
- CONSULT QUESTION: Do we need to do an MRI or can this be blamed on the risperidone alone?



Prolactin Elevation: (Pringsheim T et al. Drug Saf 2011)

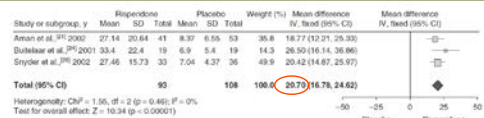


Fig. 3. Prolactin level at endpoint (ng/mL), risperidone vs placebo (randomized controlled trials <12 weeks); df = degrees of freedom; IV, inverse variance.

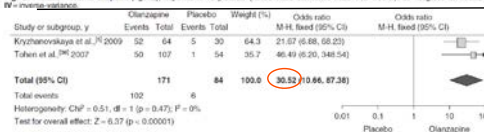


Fig. 11. Prolactin levels at any time during treatment, olanzapine vs placebo; df = degrees of freedom; M-H, Mantel-Haenszel.

Recommendations and Results

- Recommendations: removal of risperidone to r/o prolactinoma or other pituitary tumour (document PRL normalization)
- Patient was taken off risperidone for 2 weeks and labs rechecked
 - Prolactin level: 2.9 ug/L (<20 ug/L)
- Risperidone reintroduced. Next labs show prolactin of 66.1 ug/L. Counselled on Calcium/Vitamin D for bone health. Recheck prolactin as clinically indicated.



Summary of Research Findings



- Exponential rise in prescription rates of SGAs
- Limited number of indications and target symptoms for which there is evidence for their efficacy
- Incredible burden of obesity, type 2 diabetes, and the components of the metabolic syndrome putting patients at future risk for cardiovascular disease
- Once an SGA is prescribed, appropriate metabolic monitoring is required at baseline and regular intervals thereafter
- Low frequency of metabolic monitoring in the community



Clinical Implications

- It is incumbent on treating physicians to balance the risks vs. the benefits of this pharmacologic treatment
- Physicians require support to ensure SGAs are only used to target evidence-based diagnostic indications/target symptoms
- Education and resources are now available to support professionals and families directed to:
 - evidence-based prescribing practices
 - appropriate monitoring for metabolic complications
 - healthy living strategies to mitigate complications



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- Ms. Valerie Tregillus
- Dr. Margaret Weiss
- Dr. Connie Coniglio
- Dr. Dean Elise
- Dr. Derryck Smith
- Ms. Keli Anderson (The FORCE)



Thank-you!

Questions or Comments?

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