camh Centre for Addiction and Mental Health

Addressing Metabolic Comorbidities in Clients with Mental Illness: an Update

Margaret Hahn, MD, PhD, FRCPC
Mahavir Agarwal, MBBS, MD, PhD
Kelly Matheson, MSc, RD
Caroline Walker

camh

UNIVERSITY OF TORONTO

Serious Mental Illness and Cardiovascular Risk

- Mental illness and metabolic co-morbidity
- The client perspective on metabolic comorbidities
  - Caroline Walker
- Gaps in physical care and implications
- Intervention strategies: pharmacological and behavioral

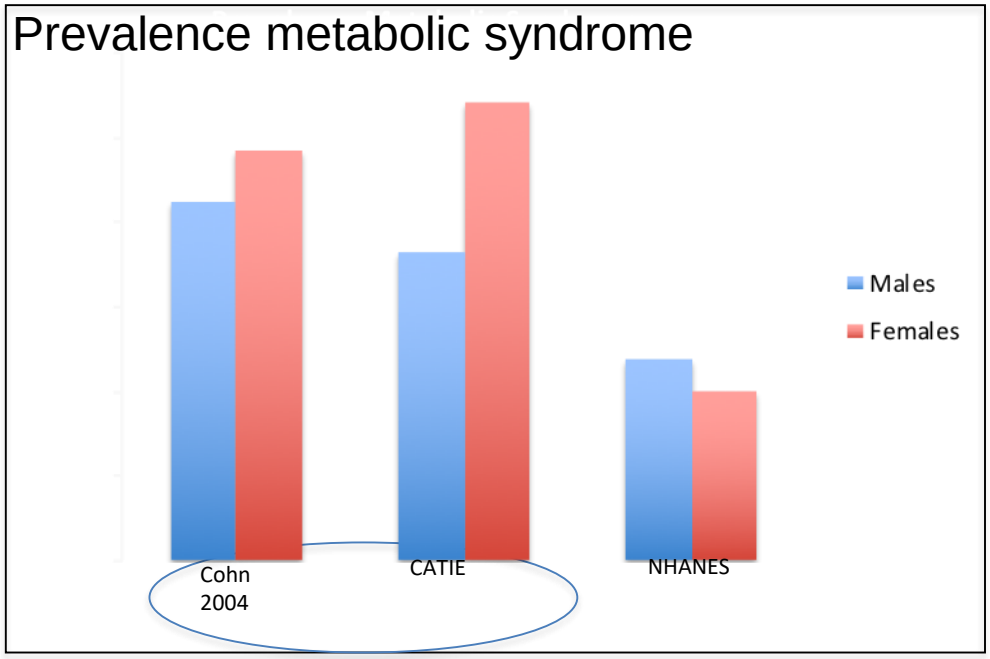
camh

Serious Mental Illness and Cardiovascular (CV) Risk

- Patients with Serious Mental Illness have a 20% reduced life-expectancy and a 2x of standardized mortality ratio from CV disease (Hennekens C 2005)

camh

Metabolic Syndrome in Severe Mental Illness



•Metabolic Syndrome (MetS) = Constellation of metabolic abnormalities:

(Glucose intolerance, Central obesity, high triglycerides, low-HDL,Hypertension)

•Associated with 3-6x increased risk of CV disease and 5-6x increased risk diabetes

McEvoy 2005, Cohn 2004

camh

Type 2 Diabetes and Mental Illness

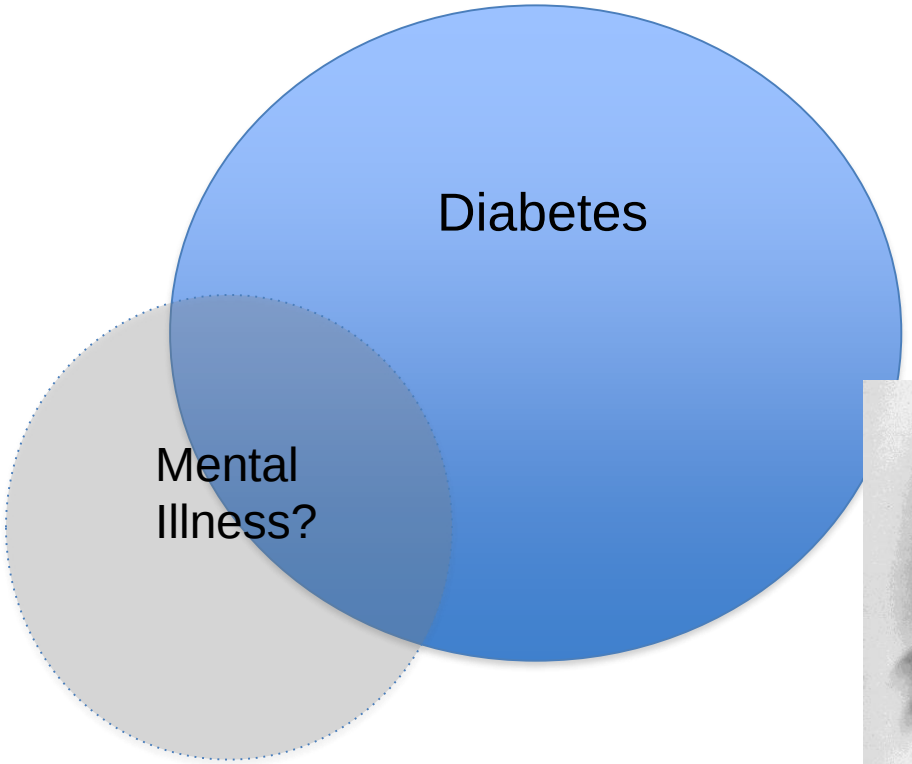
- **Type 2 Diabetes (T2DM)**:
- Increases rate CHD by 3-4 fold
- CHD occurs 10-12 years earlier

- 2-5x prevalence of Type 2 Diabetes in serious mental illness

camh

Canadian Diabetes Practice Guidelines 2013; DeHert 2006; McEvoy 2005

Diabetes and Mental Illness



"diabetes is a consequence of prolonged sorrow"
Thomas Willis, 17th century

"*diabetes is a disease which shows itself in families in which insanity prevails"*
Sir Henry Maudsley, 18th century

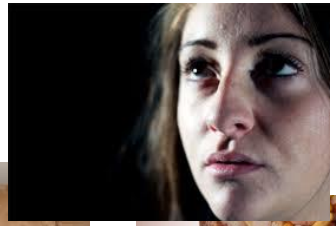
camh

Factors related to serious mental illness which increase risk of obesity/ diabetes

Mental Illness → Diabetes, Obesity, MetS

Illness biology

Genetic links with metabolic dysfunction



Life style factors:

Poor self care
High smoking rates
Inactivity
Poor dietary habits

Treatments:

Antipsychotics **
Antidepressants
Mood stabilizers

Systems factors

Reduced access to physical care
"Silo working": Poor co-ordination between health providers
Policy ambiguities

camh

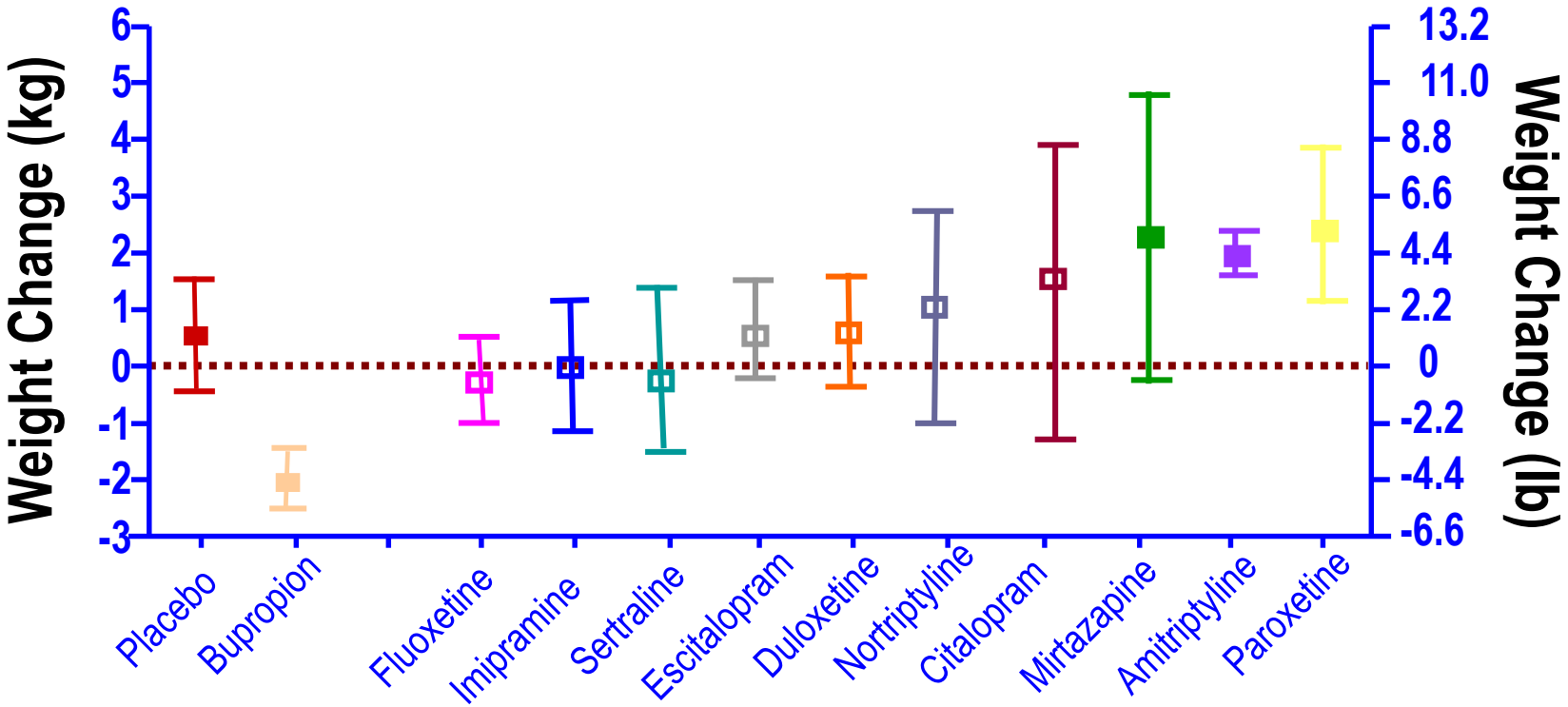
Special considerations: treatments

Table 1 – Relative incidence of weight gain with selected psychotropic medications[2,10,12-14,28-29]

Antidepressants	Relative incidence	Antipsychotics	Relative incidence	Mood stabilizers	Relative incidence
Amitriptyline	+++	Aripiprazole	+	Carbamazepine	+
Bupropion	+/–	Asenapine	+	Lamotrigine	+
Citalopram	+	Chlorpromazine	++	Lithium	++
Duloxetine	+	Clozapine	+++	Valproate	++
Escitalopram	+	Haloperidol	+		
Fluoxetine	+	Olanzapine	+++		
Mirtazapine	+++	Risperidone	++		
Paroxetine	++	Quetiapine	++		
Sertraline	+	Ziprasidone	+		
Venlafaxine	+				

+/- very low risk (or even weight loss), + low risk, ++ moderate risk, +++ high risk.

Weight Change During Maintenance Antidepressant Treatment



camh

All > 4 month data
Adapted from Serretti et al, J Clin Psych 71:10 2010

Antipsychotic (AP) drugs: widespread use beyond schizophrenia

- Approval for schizophrenia, bipolar, refractory depression, irritability in autism
- Increasingly being used off-label
  - Use of APs among children is growing, even as use of other psychotropic medications declines

Correll C 2009, 2010; Alvarez-jimenez M 2008; De Hert M 2011; Hahn M 2014

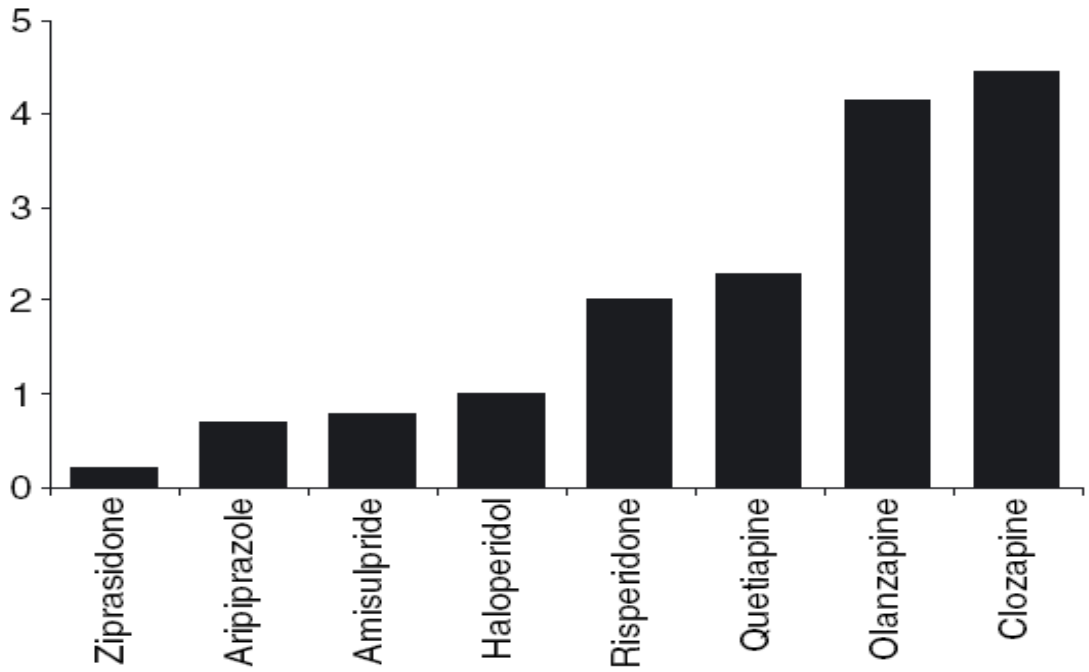
camh

‘Second generation’ antipsychotics

- Significant metabolic side-effects:
  - Weight gain
  - Insulin resistance
  - Atherogenic lipid profile

camh

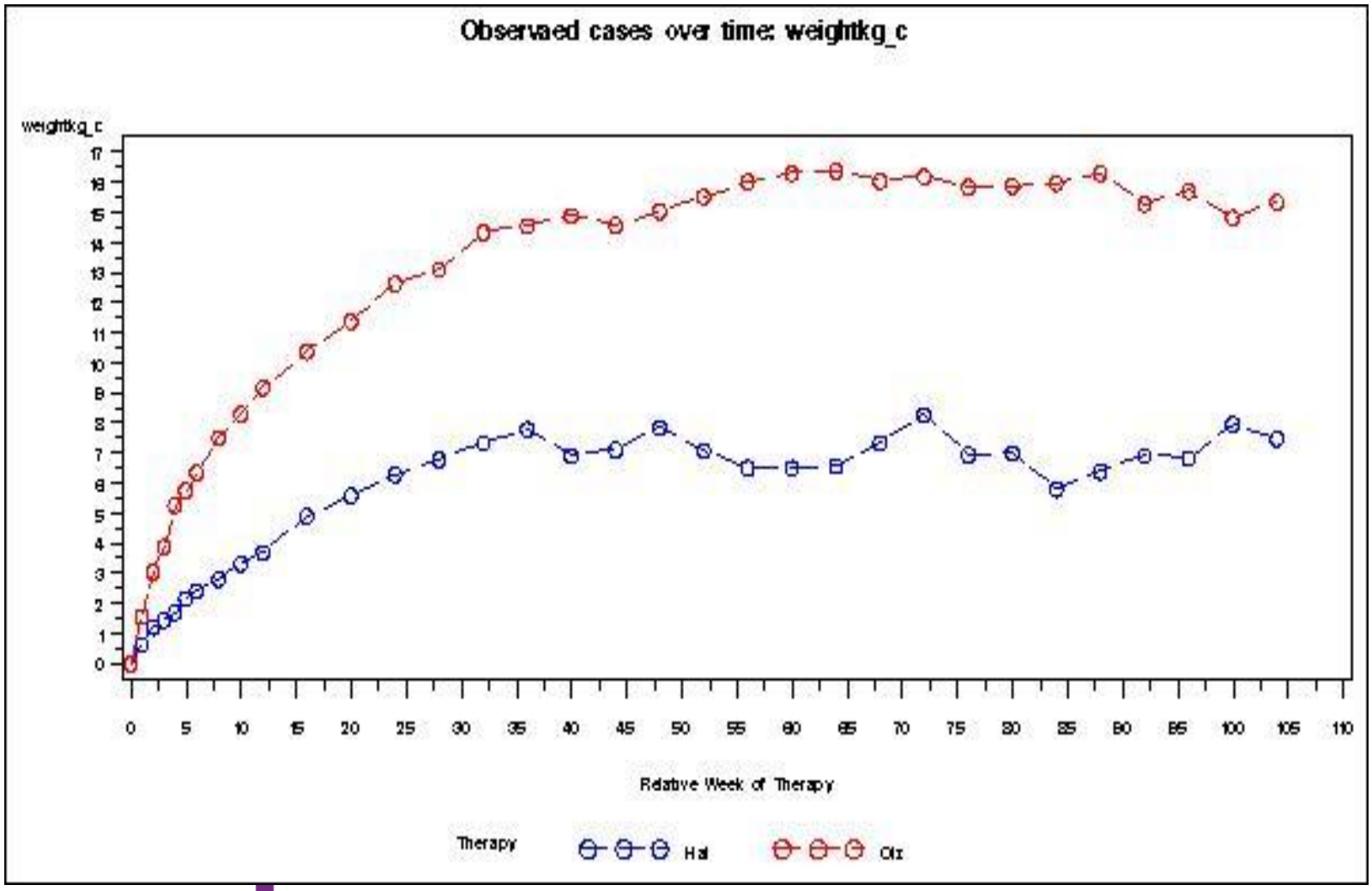
Differential Liability:
Mean Increase (Kg) in Weight at 10 Weeks



camn

Newcomer JW. CNS Drugs 2005

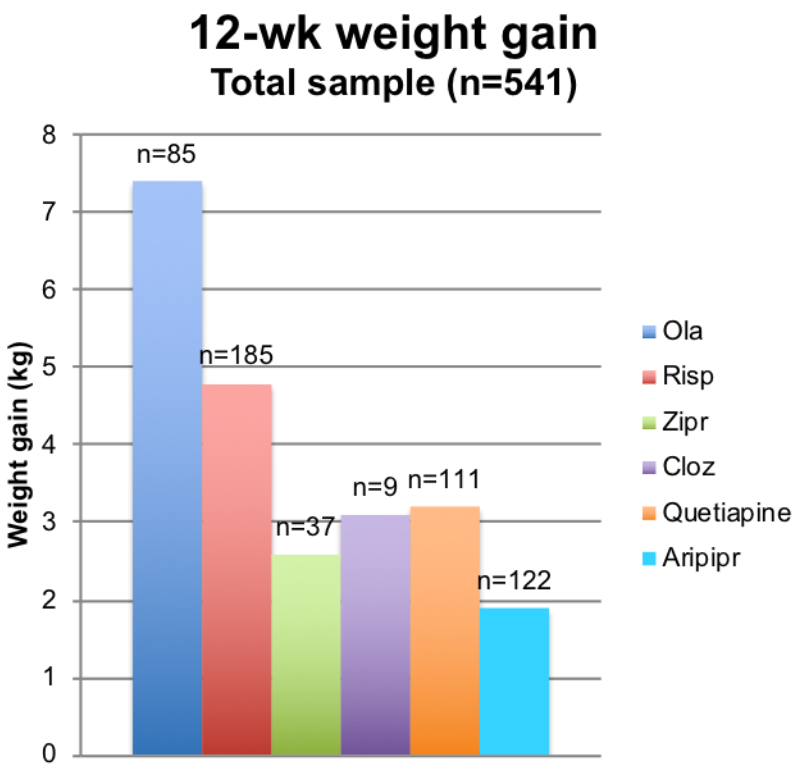
Olanzapine vs. Haloperidol: First Episode Psychosis

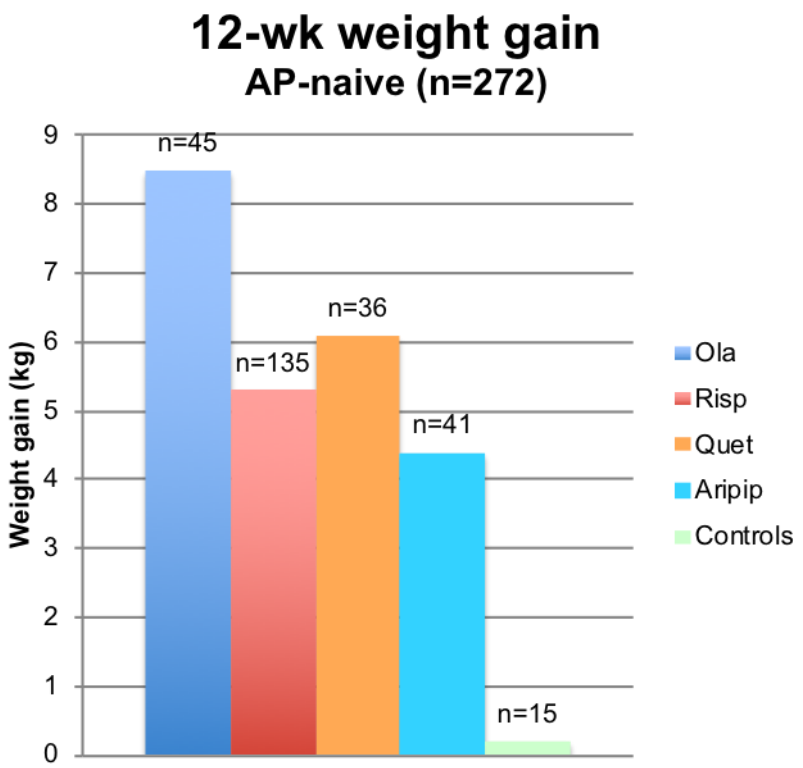


camh Slaight Family Centre for Youth in Transition

Zipursky et al. Br J Psychiatry 2005; 187:537-543

Early Episode Patients

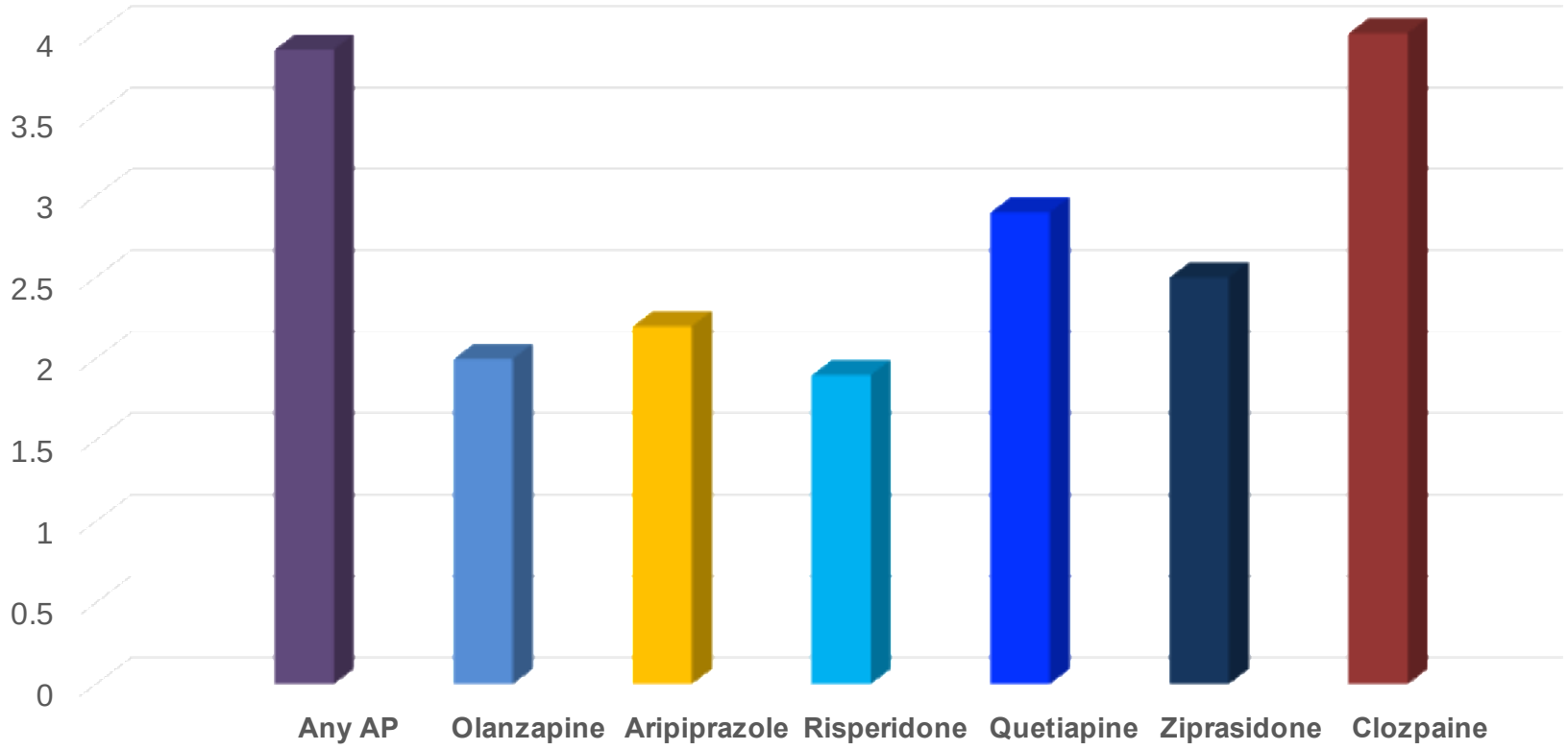




camh

Correll et al. JAMA 2009;302(16)1763

Antipsychotic(AP)-Related Risk of Diabetes in Schizophrenia



- Danish population based cohort study (all persons born 1977-2013; n= 2.7 million, 49 582279 person years); Hazard risk Diabetes after AP vs risk in AP-naïve SCZ

camh

Rajkumar A, *et al.* Am J Psychiatry 2017

Early metabolic risk accrual…..Type 2 diabetes

- Antipsychotic (AP) use in children and adolescents has been associated with 2-3 fold increase in Type 2 Diabetes
- Compared with youths only starting APs, the risk was 2 fold higher with concurrent use of antidepressants

camh

Bobo W JAMA 2013; Rubin D JAMA 2015

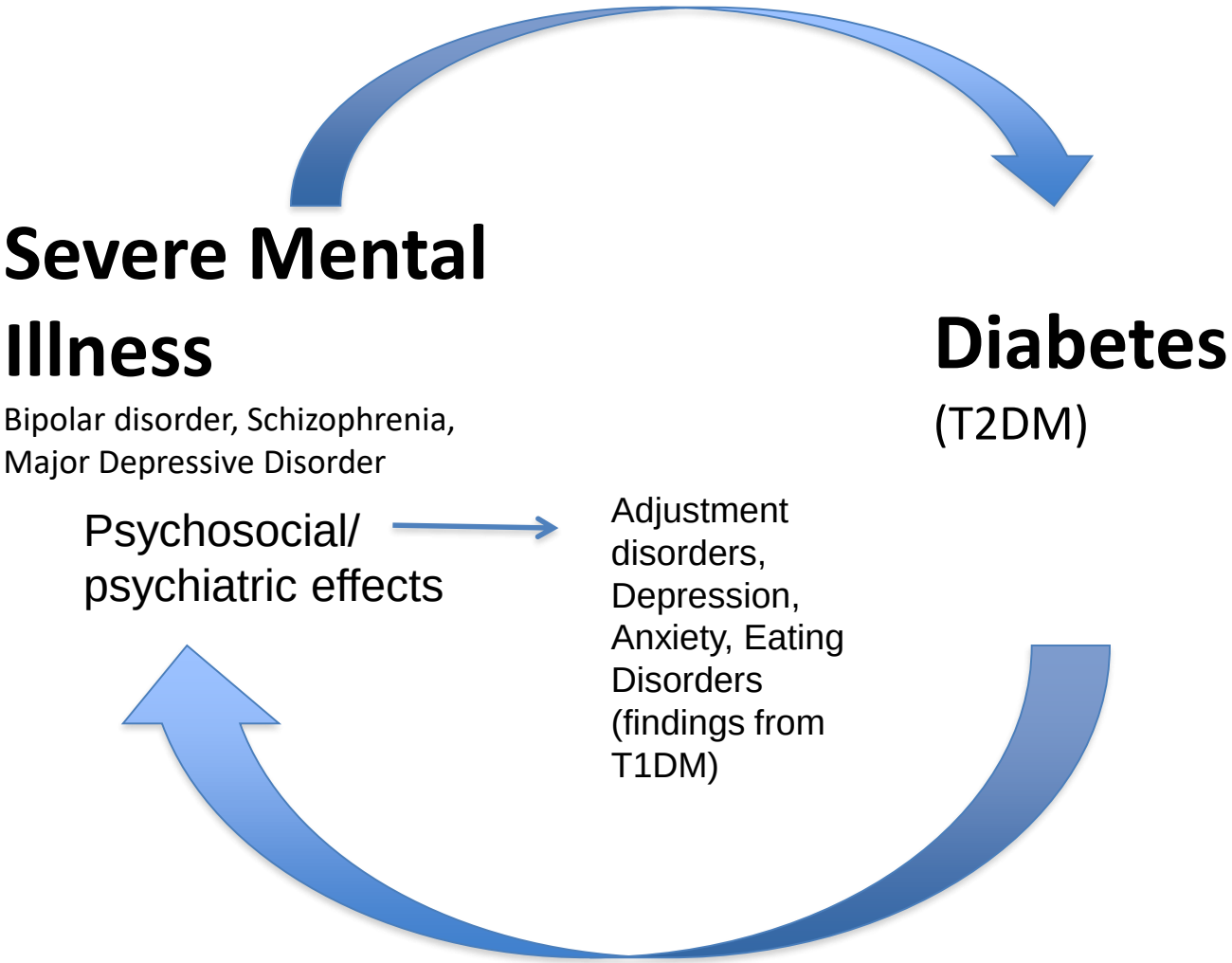
Implications (beyond CV morbidity& mortality)

- Medication compliance
- Self-esteem
- Hospitalization rates
- Quality of life
- Social retreat
- Social care costs

De Hert M, 2006; De Hert M 2007; Lyketsos C 2002; McCrone P 2008

camh

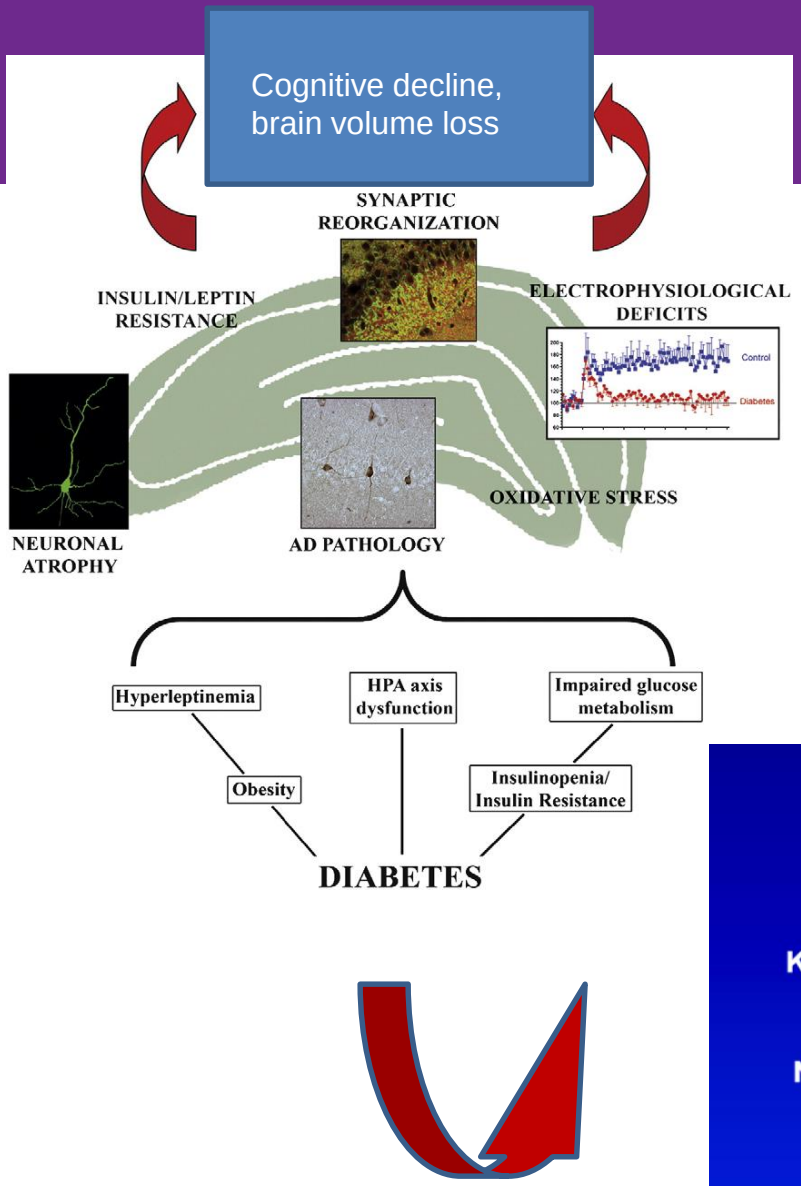
Implications: a bi-directional relationship

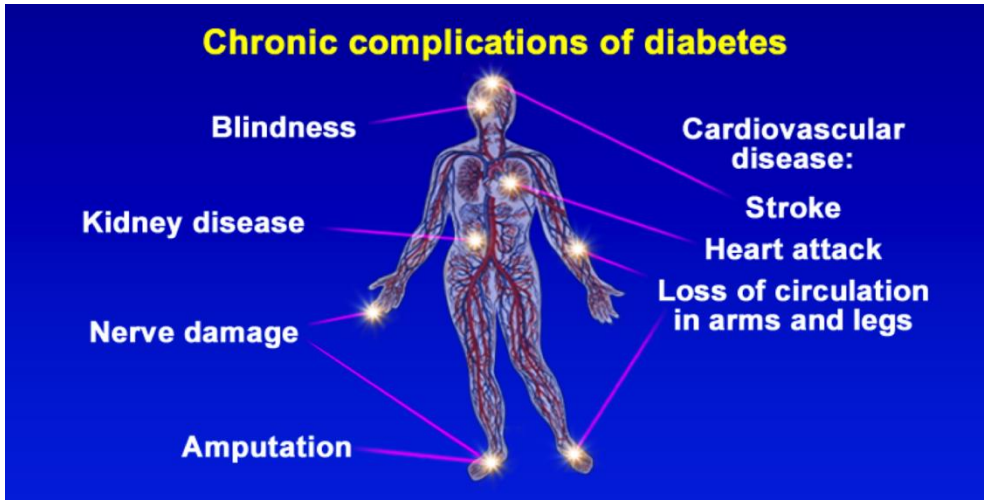


camh

Co-morbid psychiatric illness (particularly MDD) + diabetes confers worse outcomes than either alone

Diabetes, obesity & the brain





camh

Summary

- Serious mental illness is associated with high rates of metabolic comorbidity including T2D
- Metabolic risk is accrued early on
- Pathophysiology- complicated
- Psychotropic agents contribute through largely unknown mechanisms

camh

A client perspective….

- Caroline Walker

  The impact of these comorbidities on the lives of patients with mental illness, and their family members and caregivers

camh

Addressing the gaps….

camh

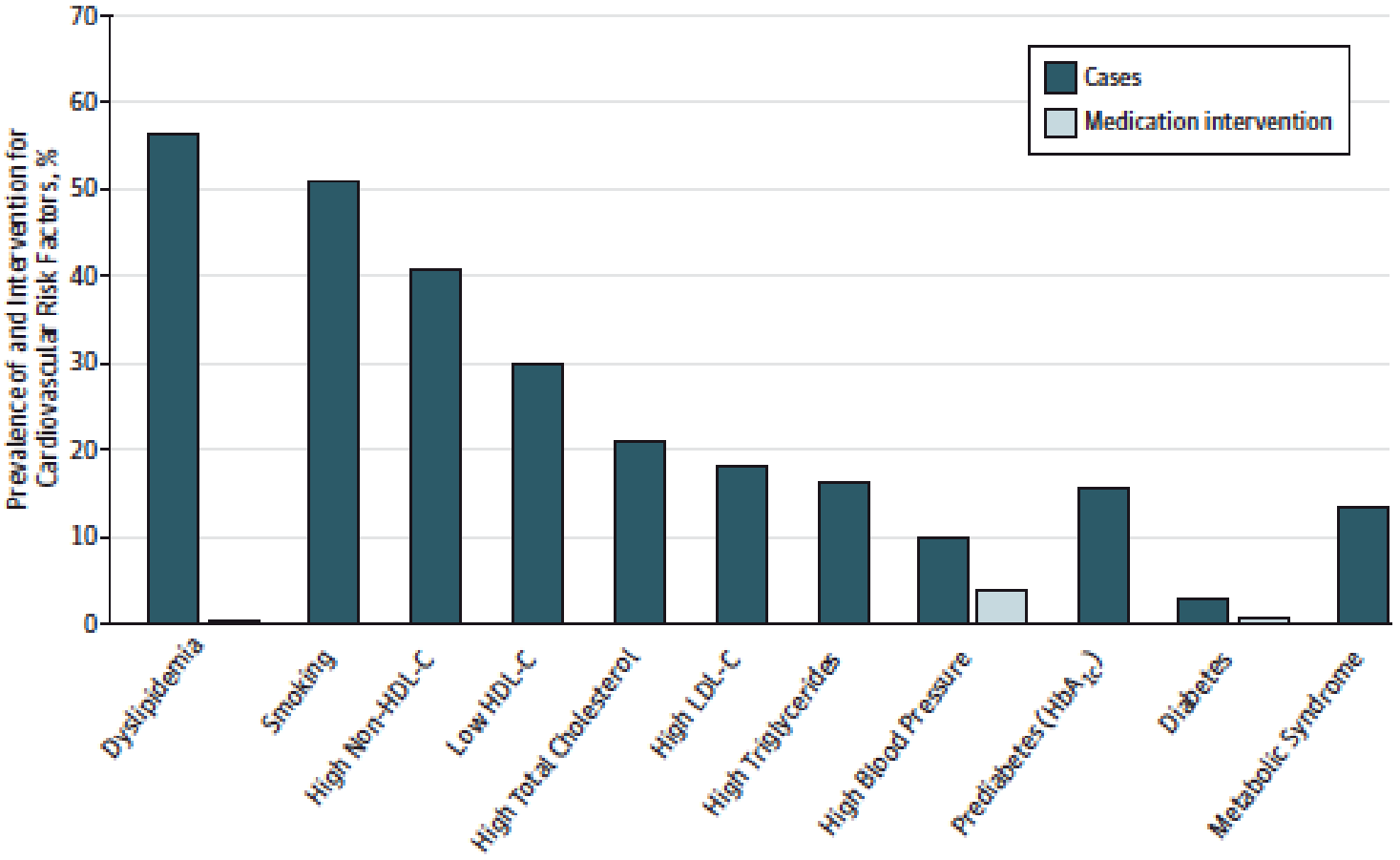
Disparities in Care: Screening/ monitoring

- Data comparing large groups of controls to those with psychosis taking psychotropics show low rates of monitoring

camh

Barnes TR 2007; Lambert TJ 2009; Haupt D 2009

First episode patients : Prevalence of CV risk factors and respective medical treatment



camh

Correll CU, JAMA 2014

Interventions….

- Underlying causes of metabolic co-morbidities may be different in those with SMI vs. general population
- This may mean treatments may not work in the same way
- Paucity of studies looking at interventions outside of weight gain

Medication-induced weight gain:

- Possible strategies:
  - Dose reductions
  - Switching
  - Non-pharmacological interventions
  - Pharmacological compounds

camh

Lowering dose

- Paucity of data
  - Small signal between serum concentrations of olanzapine and clozapine (Simon VJ 2009)
  - Less evidence for association with dose (Simon VJ 2009)
  - Varying dosage of olanzapine w/i therapeutic range appears to have no significant impact on weight gain (Perry PJ 2005)

Simon V J *et al.* Clin Psych 2009

Switching strategies

- Systematic review (4 studies, n=636):
  - Olanzapine → Aripiprazole /Quetiapine
    - Mean weight loss of 1.94 kg (2 RCT, n = 287)
    - Fasting blood glucose decrease when switched to aripiprazole or quetiapine from olanzapine (2 RCT, MD -2.53 n = 280)
    - Less likely to leave the study early if remain on olanzapine
    - No significant difference in mental state, adverse events

camh

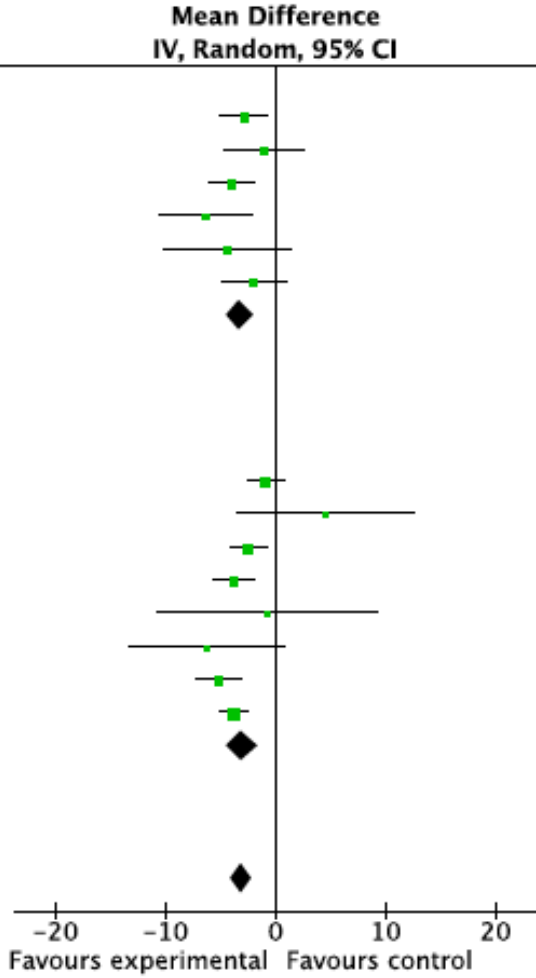
Mukundan et al. 2010

Behavioral Interventions

- **CBT**: psychoeducation, self-monitoring, teaching behavioral change strategies, cognitive restructuring
- **Nutritional/ and or exercise interventions**: supervised exercise programmes, psychoeducation regarding healthy lifestyle, and or nutritionist/ dietician consults

Behavioral Interventions (17 RCTs)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.59.1 Prevention trials								
Alvarez-Jimenez 2006	4.1	3.99	28	6.98	4.5	33	9.6%	-2.88 [-5.01, -0.75]
Cordes et al 2011	3.4	4.2	13	4.5	6.1	18	4.8%	-1.10 [-4.73, 2.53]
Evans 2005	2	3.6	23	6	2.6	11	9.7%	-4.00 [-6.13, -1.87]
Littrell 2003	0.81	8.97	35	7.17	9.16	35	3.8%	-6.36 [-10.61, -2.11]
Poulin 2007	84.4	18.2	59	88.8	12.3	51	2.3%	-4.40 [-10.14, 1.34]
Scocco 2005	0.99	3.34	10	2.96	3.08	8	6.4%	-1.97 [-4.94, 1.00]
Subtotal (95% CI)			**168**			**156**	**36.6%**	**-3.23 [-4.41, -2.04]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.87$, df = 5 (P = 0.43); $I^2 = 0\%$								
Test for overall effect: Z = 5.35 (P < 0.00001)								
1.59.2 Intervention trials								
Brar 2005	-2	3.79	34	-1.1	3.11	37	12.4%	-0.90 [-2.52, 0.72]
Khazaal 2007	88	14.9	31	83.5	17.2	30	1.2%	4.50 [-3.59, 12.59]
Kwon 2006	-3.94	3.63	29	-1.48	1.88	14	12.2%	-2.46 [-4.11, -0.81]
Mauri 2008	-3.6	2.6	15	0.2	2.9	18	10.9%	-3.80 [-5.68, -1.92]
McKibbin 2006	98.5213	21.228	28	99.2924	16.919	29	0.8%	-0.77 [-10.76, 9.22]
Weber 2006	84.1848	6.54236	8	90.4667	7.35393	7	1.5%	-6.28 [-13.37, 0.81]
Wu 2007	-4.2	4.4	28	1	3.4	25	9.8%	-5.20 [-7.31, -3.09]
Wu 2008	63.4	2.6	32	67.2	2.6	32	14.5%	-3.80 [-5.07, -2.53]
Subtotal (95% CI)			**205**			**192**	**63.4%**	**-3.04 [-4.39, -1.68]**
Heterogeneity: $Tau^2 = 1.82$; $Chi^2 = 17.54$, df = 7 (P = 0.01); $I^2 = 60\%$								
Test for overall effect: Z = 4.40 (P < 0.0001)								
Total (95% CI)			**373**			**348**	**100.0%**	**-3.12 [-4.03, -2.21]**
Heterogeneity: $Tau^2 = 1.08$; $Chi^2 = 22.46$, df = 13 (P = 0.05); $I^2 = 42\%$								
Test for overall effect: Z = 6.69 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0\%$								



camh

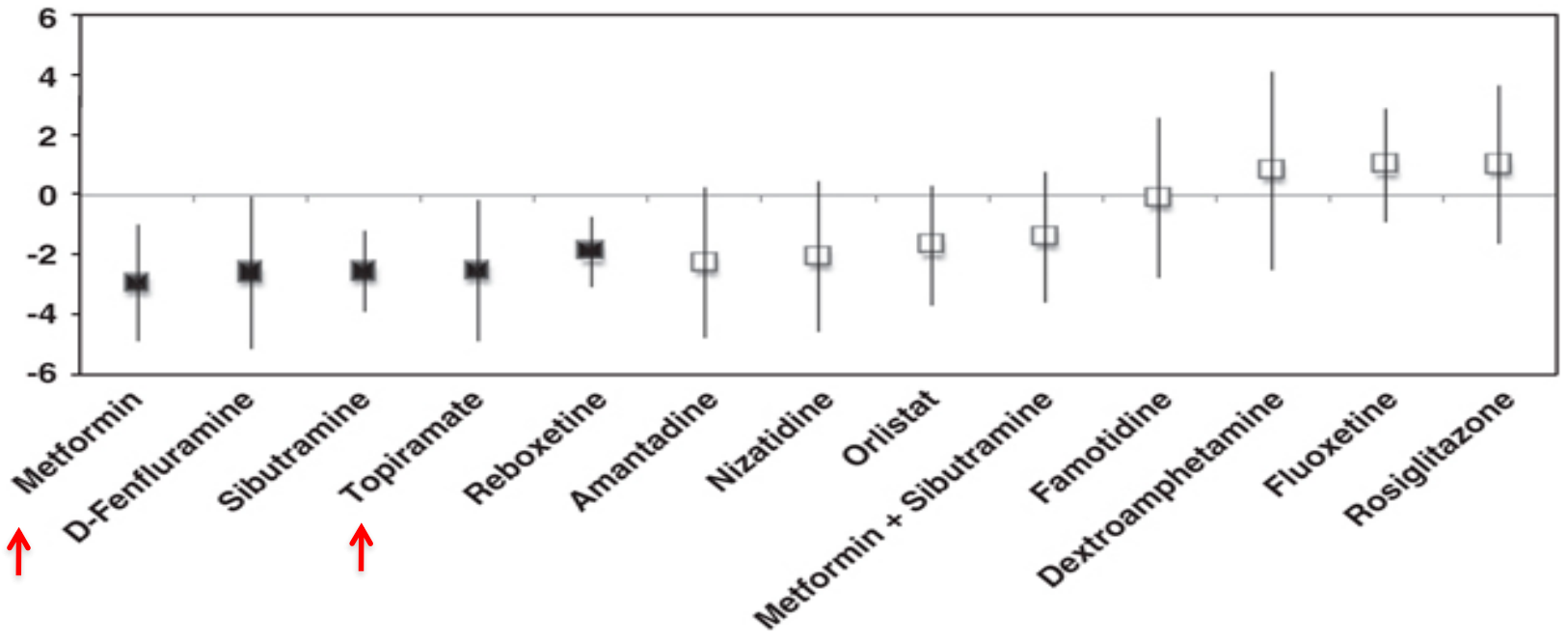
Caemmerer J et al. 2012

Pharmacological Interventions for Weight Loss

- Agents indicated for weight loss & available in Canada:
  - Orlistat (lipase inhibitor)
  - Saxenda (GLP-1R agonist)
  - Contrave (Naltrexone-bupropion)

camh

Pharmacological Interventions



Weighted mean difference with 95% CI of weight change in Kg b/w PL and treatment

(Maayan L 2010; Neuropsychopharmacology 35:1520)

camh

Cochrane meta-analysis: Pharmacological interventions for antipsychotic induced weight gain (AIWG)

- Update to 2007 Cochrane review (Faulkner *et al*.)
- Weight loss (treatment) or maintenance (prevention) must be primary outcome

camh

Hahn M, Agarwal M, *et al*. In preparation

Prevention of AIWG

- The following compounds were studied (number of studies in brackets)

Metformin (4)	**Topiramate (1)**	Fluoxetine (1)
Reboxetine (1)	Famotidine (1)	Reboxetine betahistidine (1)
Nizatidine (1)		

camh

Agarwal M, *et al*. In preparation

Summary: Prevention AIWG

- Metformin found to be effective in preventing weight gain
- Single study found topiramate to be effective
- No significant tolerability/side effect concerns or worsening of mental status with any of the drugs

camh

Agarwal M, *et al*. In preparation

Treatment: Antipsychotic-induced weight gain (AIWG)

- The following compounds have been studied:

Metformin (11)	**Sibutramine (3)**	**Nizatidine (3)**
Aripiprazole (2)	**GLP-1RAs (3)**	Fluoxetine (1)
Topiramate (1)	Phenylpropanolamine (1)	DHEA (1)
Orlistat (1)	Naloxone (1)	Rimonabant (1)
Metformin sibutramine (1)	Modafinil (1)	Rosiglitazone (1)
Ramelton (1)	Atomoxetine (1)	Dextramphetamine (1)
Saffron extract (1)	Intranasal insulin (1)	Celery, dill, green tea (1)
Amantadine (2)		

camh

Hahn M, Agarwal M *et al*. In preparation

Summary: Treatment of AIWG (off-label)

- **Metformin** found to be bring about adaptive change in multiple metabolic parameters
- **Topiramate** and **GLP-1RAs**- may be helpful
- **Aripiprazole** (in clozapine-treated patients) and **nizatidine** found to reduce weight (poor quality studies)
- No significant tolerability/side effect concerns or worsening of mental status with any of the drugs

camh

Hahn M, Agarwal M, *et al*. In preparation

Weight loss medications (FDA approved)

Newer drugs:

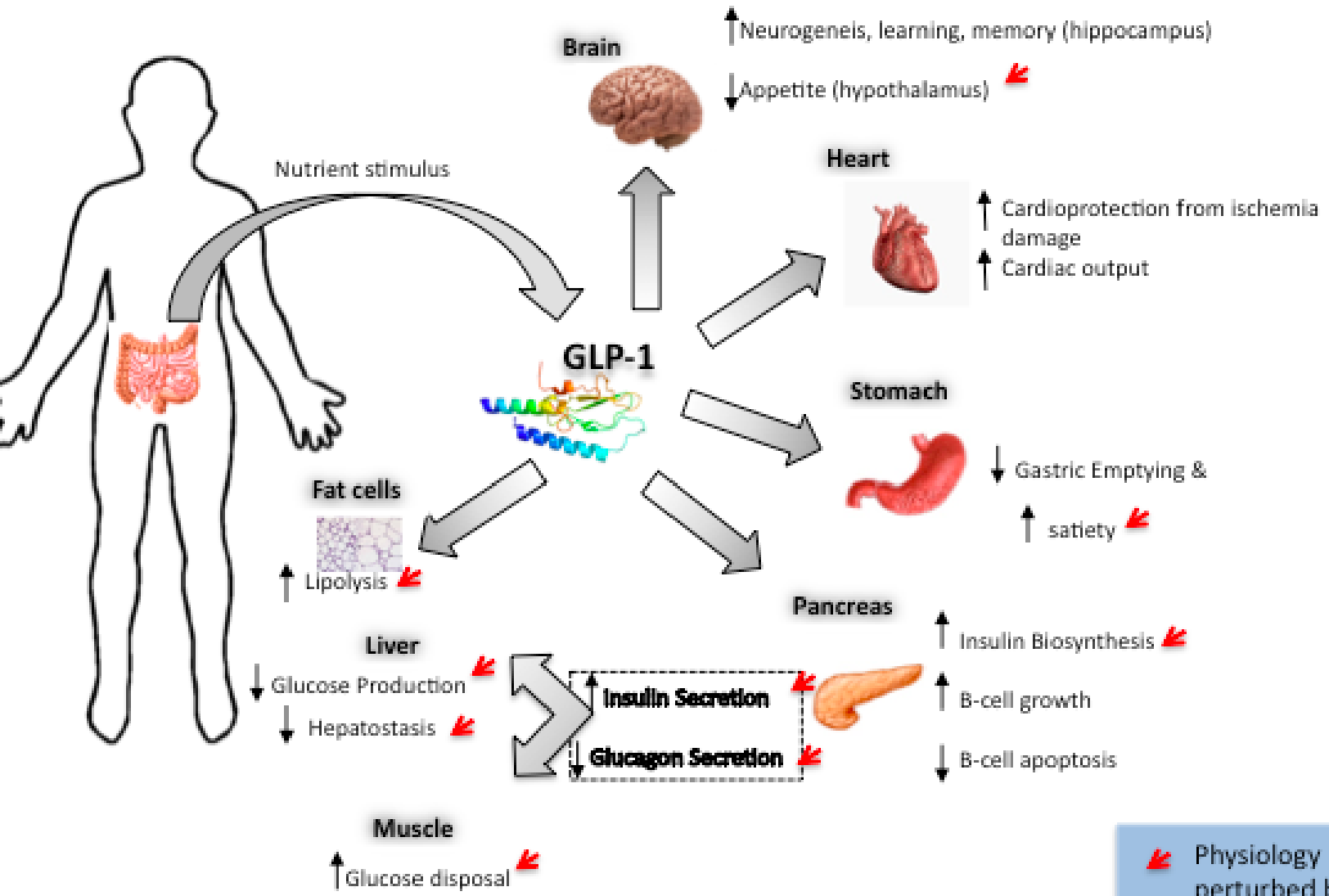
- Locaserin (Belviq) : 5HT2C agonist
- Naltrexone-bupropion (Contrave)
- Phenteramine topiramate (Qysmia)

camh

Monsters, madness and metabolism …

camh

GLP-1R agonists for metabolic and mental health?



Adapted from Baggio & Drucker, 2007

GLP-1 RA for antipsychotic-associated cardio-metabolic risk factors

- A systematic review and individual participant data meta-analysis (3 RCTs)

Author year	Location	Duration	GLP-1-RA Agent	frequency	Control	Included antipsychotics	Number of Participants (GLP-1-RA / Control)	% completed (GLP-1-RA / Control)
Ishoy et al 2017	Denmark	12 weeks	Exenatide 2mg s/c weekly	weekly	placebo	All antipsychotics	23 / 22	87.0% / 90.9%
Larsen et al 2017	Denmark	16 weeks	Liraglutide 1.8mg s/c daily	daily	placebo	Clozapine and olanzapine	47 / 50	90.3% / 98.0%
Siskind et al 2017	Australia	24 weeks	Exenatide 2mg s/c weekly	weekly	Usual care	Clozapine	14 / 14	100% / 100%

camh

Siskind, Hahn, *et al*. Diab Obes Met. 2018

Outcomes:

Variable*	N	Mean Difference GLP-1RA vs control	SE	Treatment effect		Study Effect	
				F value	Sig	F value	Sig
Weight (kg)	168	-3.71	0.65	33.19	<0.001	0.85	0.430
Waist (cm)	167	-3.00	0.68	19.24	<0.001	2.05	0.132
BMI (kg/m^2)	168	-1.19	0.22	30.25	<0.001	1.13	0.326
HbA1c (IFCC)	166	-3.25	0.66	24.54	<0.001	1.28	0.281
FBG (mmol/L)	166	-0.45	0.09	24.89	<0.001	1.54	0.218
HDL (mmol/L)	166	-0.01	0.02	0.33	0.566	2.92	0.034
TG (mmol/L)	166	-0.24	0.12	3.73	0.055	0.68	0.508
SBP (mmHg)	160	-1.89	1.61	1.39	0.241	0.94	0.392
DBP (mmHg)	160	-1.91	1.17	2.68	0.104	5.84	0.004
HOMA	125	-1.00	0.73	1.88	0.172	1.55	0.216
Insulin (mU/L)	125	-0.62	2.32	0.07	0.791	0.64	0.425
Android/gynoid ratio	131	-0.006	0.014	0.16	0.692	0.002	0.963
Visceral fat (gm)	97	-177.51	68.71	6.67	0.011	2.92	0.091

camh

Siskind, Hahn, *et al*. Diab Obes Met. 2018

Moving beyond weight gain?

camh

Type 2 Diabetes and Severe Mental Illness (SMI)

- No existing intervention studies in AP-users/ serious mental illness and Type 2 Diabetes
- Large diabetes intervention trials systematically exclude individuals with SMI

camh

Treatment of dyslipidemias in SMI

- Statins:
  - 1 RCT, small observational trial, open-label study , 1 cohort analysis
- Support effects on T-chol and LDL

camh

De Hert M et al 2006; Vincenzi B et al 2014; Blackburn R et al 2017

Summary: interventions

- Paucity of studies examining interventions (outside of weight gain)
  - No single agent has “indicated” use for psychotropic induced weight gain
  - Need to examine effects on long-term CV outcomes
- Inherent differences in our patients vs. non-mentally ill ?

camh

General recommendations

- Psychoeducation
- At a minimum, screen and and treat to the same targets as the general population

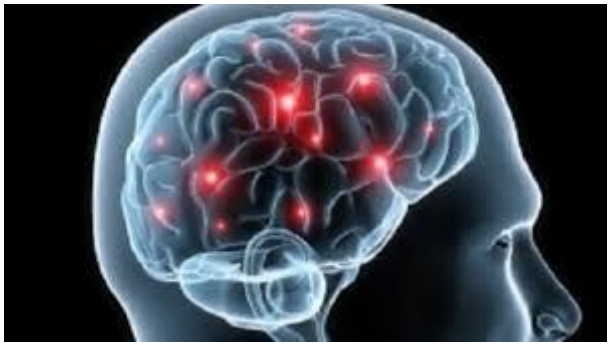
Metabolic monitoring

Parameter	Base-line	1 mo	2 mos	3 mos	Every 3-6 mos	Annually
Weight (BMI)	X	X	X	X	X	
Waist circumference	X			X		X
Blood pressure	X			X		X
Fasting plasma glucose and/or A1C	X			X	X	
Lipid profile	X			X	X	
Personal history of alcohol, tobacco, recreational drug use	X			X		X
Family history	X					X

camh

General Recommendations: starting AP medications

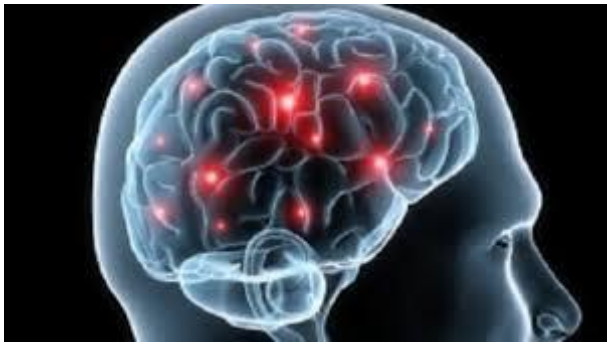
- Avoid “off-label” antipsychotic use
- If unavoidable, use on short-term basis and reassess need regularly



https://choosingwiselycanada.org/psychiatry/

General Recommendations: starting AP medications

- Avoid drugs more likely to cause metabolic side-effects when new treatments are initiated “on-label”
  - First episode patients are at highest risk



De Hert M et al. British J Psych 2011 (199): 99

Interventions

- Diet and exercise intervention should be front-line
- Smoking cessation

camh

Nutrition at CAMH

Nutrition and Mental Health: What does the Research Say?

Research is looking at many areas, including:

✓Nutrition as a modifiable risk factor in the **prevention** of mental illness

✓Nutrition in the **management** of complex mental illness (currently complimentary in addition to medication and psychological interventions)

✓Underlying nutritional factors in mental illness
- ✓Low grade inflammation
- ✓Nutrient deficiencies
- ✓Dietary patterns
- ✓Gut health

camh

"I am a comfort food eater. I think that food is not just meant to stay alive. It's meant to be something that you engage in and bring peace to your mind, and to comfort you, to relax you. With my mental illness, you know sometimes I get stressed and stuff and food really calms me down."

-Research participant, Healthy Eating in Persons with Serious Mental Illnesses: Understanding and Barriers

camh

Common Nutrition-Related Issues in Serious Mental Illness (SMI)

- Medication Side effects
- Other medical diagnoses (diabetes, heart disease)
- Delusions, hallucinations, food phobias
- Disordered eating/emotional eating
- Developmental delay, cognitive deficits
- Food insecurity
- Substance use/addictions

camh

Counselling Ideas for Patients with SMI

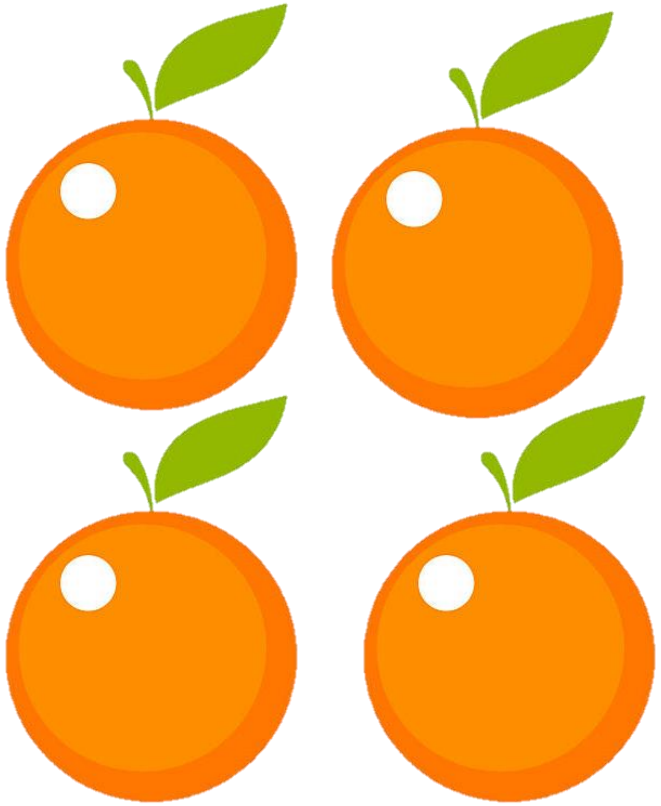
- **Goal setting:** Clear, concise, SMART, collaborative (success is more likely if the goal comes from the patient versus health-care provider)
- **Encourage small changes, with big impacts**
- If the patient is “stuck”, consider the purpose of goal setting: Small changes to improve self-efficacy compared to substantial changes that improve clinical outcomes
- **Health is not just the number on the scale:** Educate on key role of nutrition to support improvements in mood/energy, (e.g. help produce serotonin, or to counter effects of low blood sugar)
- If a patient does not express an interest or desire to address nutrition or healthy eating (and is capable/stable), respect their decision. Often physical health is placed on the backburner, and mental health takes priority. Consider these conversation starters:

•Do you find meeting with me helpful?
•What else do you need to work on first?
•I am here to listen and provide support

camh

Small Changes, Big Impacts

=



camh

Unique Challenges with Nutrition Education and Mental Health

- The ability to absorb and retain information may be challenging
- High number of developmental delay (dual diagnosis, substance use, dementia)
- Housing situations may be unique (boarding homes, supportive housing)
- Fluctuating mental state
- Negative symptoms of schizophrenia, severe depression: how do you motivate?
- Lack of social supports- mistrust of the healthcare systems, stigma of mental health
- Active concurrent substance use- even if mental illness is treated, having an addiction makes it difficult for clients to adhere to healthful behaviours
- Years of being on an inpatient unit- how do you establish a new routine?
- Inpatient diets do not necessarily reflect updated nutrition research- budget constraints

camh

A Walk a Day

camh

Interventions for psychotropic induced weight gain

- Dose reductions generally not supported
- Switching strategies can be considered

camh

Interventions

- Adjunctive pharmacological approaches may be considered if behavioral approaches fail
  - Off label:
    - Metformin (750-1000mg) *** most evidence
    - Topiramate (100-200mg)
  - Promising early evidence for GLP-1RAs

Resources to help with metabolic care:

camh

Mental Health and Metabolism Clinic at CAMH

Mental Health and Metabolism Clinic

- Any clients (from CAMH or the community):
  - Suffer from mental illness
  - Who are at risk for or have experienced weight gain, and/or other metabolic comorbidities
- Review of psychiatric medications
- Recommendations (behavioral, pharmacological)

camh

Collaborative Care Metabolism Clinic: the why

- Several of our clients fall through the cracks in our system
- Don’t have family doctor
- Who monitors and who treats
- Seen alongside a family physician (Dr. Sandeep Dhillon)

camh

Mental Health and Metabolism Clinic

Referral :

-through “Access CAMH”

-Available on-line through CAMH website:

http://www.camh.ca/en/hospital/Referrals_to_CAMH/Documents/CAMH_Referral_Form.pdf

-Any clinician can refer

camh

Acknowledgements

Banting & Best Diabetes Centre
UNIVERSITY OF TORONTO

Funding acknowledgements

Banting Foundation Early Researcher Award

University of Toronto, Department of Psychiatry Excellence Funds

Banting and Best Diabetes Centre Diabetes Scholar Award

Banting and Best New Investigator Award

Canadian Institutes of Health Research

American Academy of Child and Adolescent Psychiatry

Slaight Family Foundation

BANTING
RESEARCH FOUNDATION

Psychiatry
UNIVERSITY OF TORONTO

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada