

#NAMIcon16

Weighty Issues with Psychotropic Use in Adolescents and Young Adults

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mental HEALTH



Table 1. Observed Deaths, Years of Potential Life Lost per Death, Mortality Rates, and Standardized Mortality Ratios of Adult Medicaid Beneficiaries Diagnosed as Having Schizophrenia by Disease Category and Sex (January 1, 2001, to December 31, 2007)^a

Cause of Death	Total				Male		Female	
	Observed Deaths	Potential Life Lost per Death, Mean, y	Mortality Rate	SMR (95% CI)	Mortality Rate	SMR (95% CI)	Mortality Rate	SMR (95% CI)
All causes	74 003	28.5	1539.5	3.7 (3.7-3.7)	1576.3	3.3 (3.3-3.3)	1497.0	4.3 (4.3-4.4)
Natural death	55 741	27.0	1159.6	3.3 (3.3-3.3)	1152.1	3.0 (3.0-3.0)	1168.2	3.7 (3.7-3.8)
Cardiovascular disease	19 381	26.8	403.2	3.6 (3.5-3.6)	416.6	3.1 (3.0-3.1)	387.7	4.6 (4.5-4.7)
Ischemic heart	10 006	26.8	203.2	2.7 (2.6-2.8)	228.0	2.1 (2.0-2.2)	188.4	5.2 (5.0-5.4)

Olfson et al. *JAMA Psychiatry*.doi:10.1001/jamapsychiatry.2015.1737



What are the Causes of Morbidity and Mortality in People with Serious Mental Illness?

While suicide and injury account for about 30-40% of excess mortality, about 60% of premature deaths in persons with schizophrenia are due to “natural causes”

- Cardiovascular disease
- Diabetes
- Respiratory diseases
- Infectious diseases



Cardiovascular Disease (CVD) Risk Factors

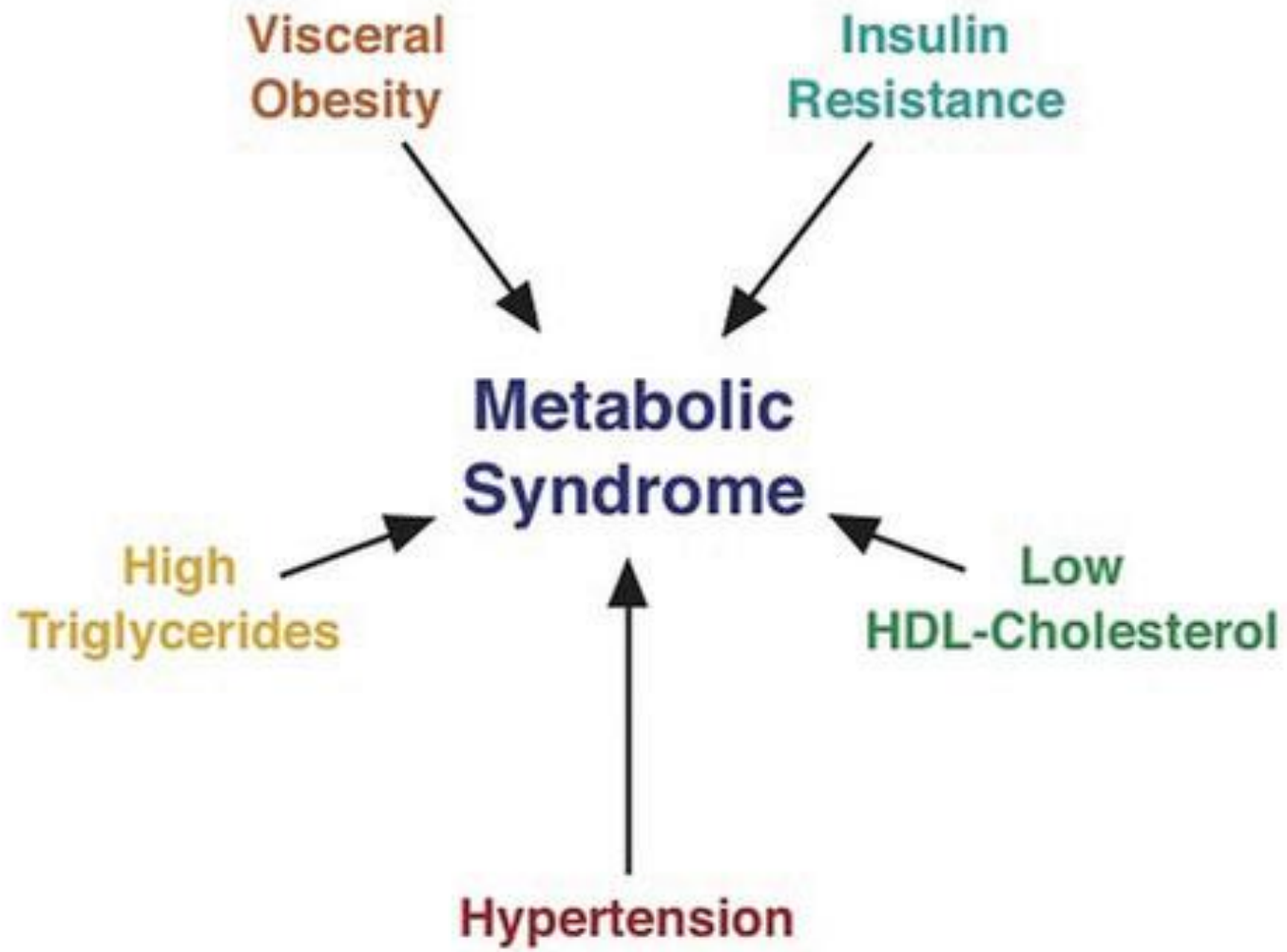
Modifiable Risk Factors	Estimated Prevalence and Relative Risk (RR)	
	Schizophrenia	Bipolar Disorder
Obesity	45–55%, 1.5-2X RR ¹	26% ⁵
Smoking	50–80%, 2-3X RR ²	55% ⁶
Diabetes	10–14%, 2X RR ³	10% ⁷
Hypertension	≥18% ⁴	15% ⁵
Dyslipidemia	Up to 5X RR ⁸	



Risk Factors & Behaviors for Cardiovascular Disease

- (+) family history for CVD
- Increasing age
- Male sex
- Blood pressure (BP)/hypertension
- Lipids/dyslipidemia
- Diabetes mellitus
- Metabolic syndrome
- Inflammation
- Physical inactivity/sedentary lifestyle
- Diet/food preferences
- Obesity
- Cigarette smoking



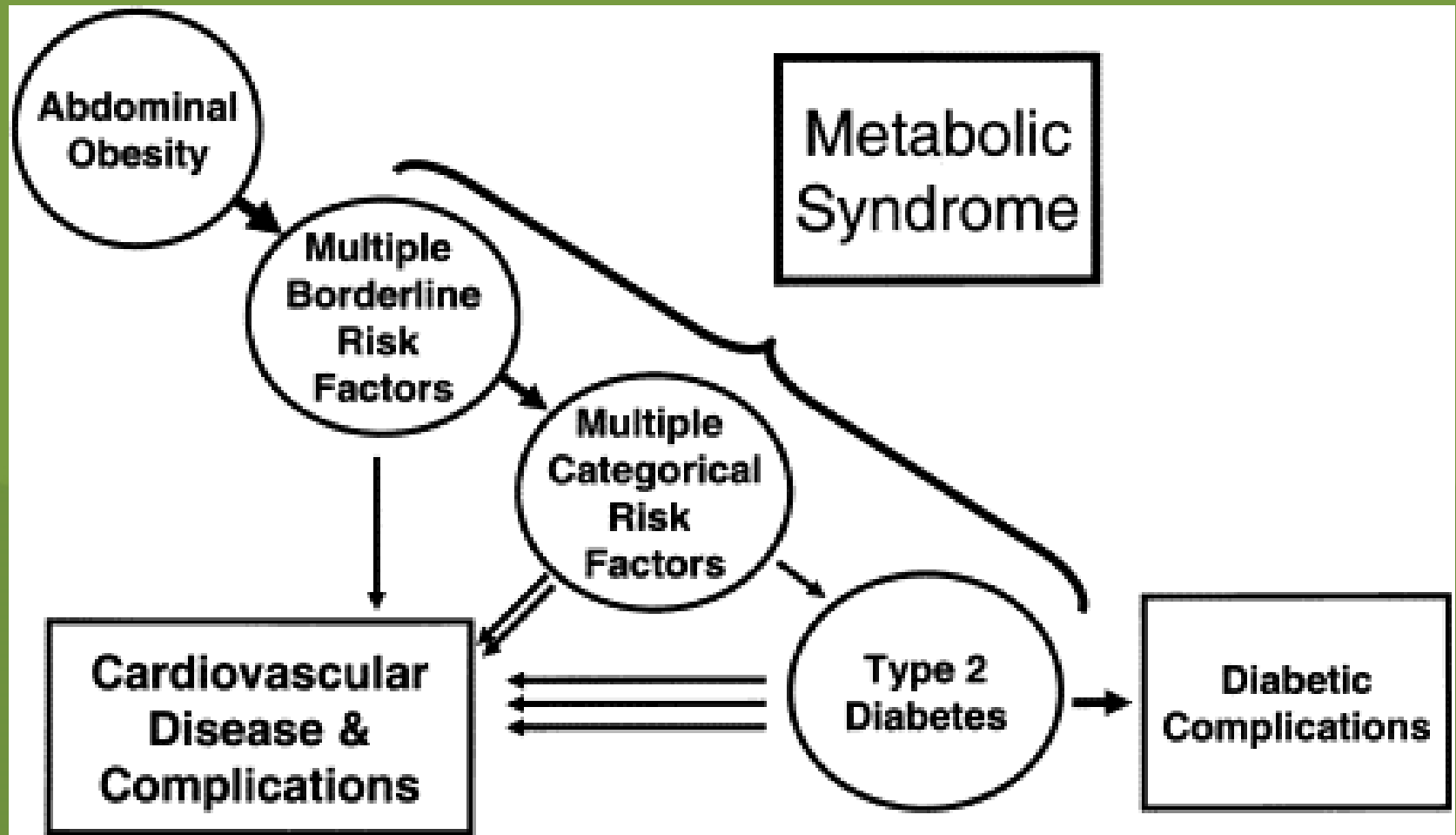


Metabolic Syndrome

- Metabolic Syndrome observed among 42.7% of 689 assessable CATIE participants
- Three of five criteria:
 - **Abdominal obesity** (waist circ. >40" men, 35" in women (39%)
 - **Fasting TG >150 ng/dl** (58.3%)
 - **HDL <40 men, <50 women** (26.5%)
 - **BP >130/85** (45.9%)
 - **Fasting Glucose >100 mg/dl** (26.5%)



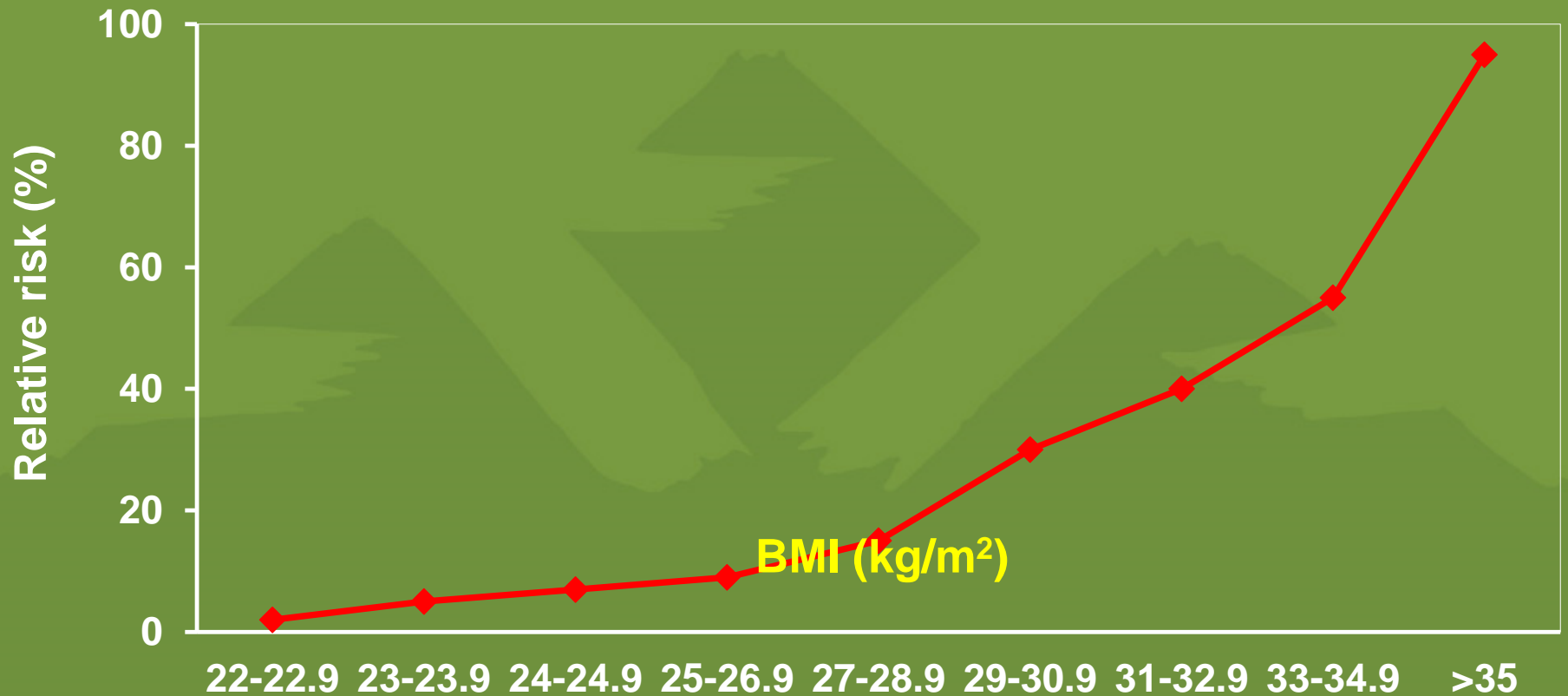
Metabolic Syndrome



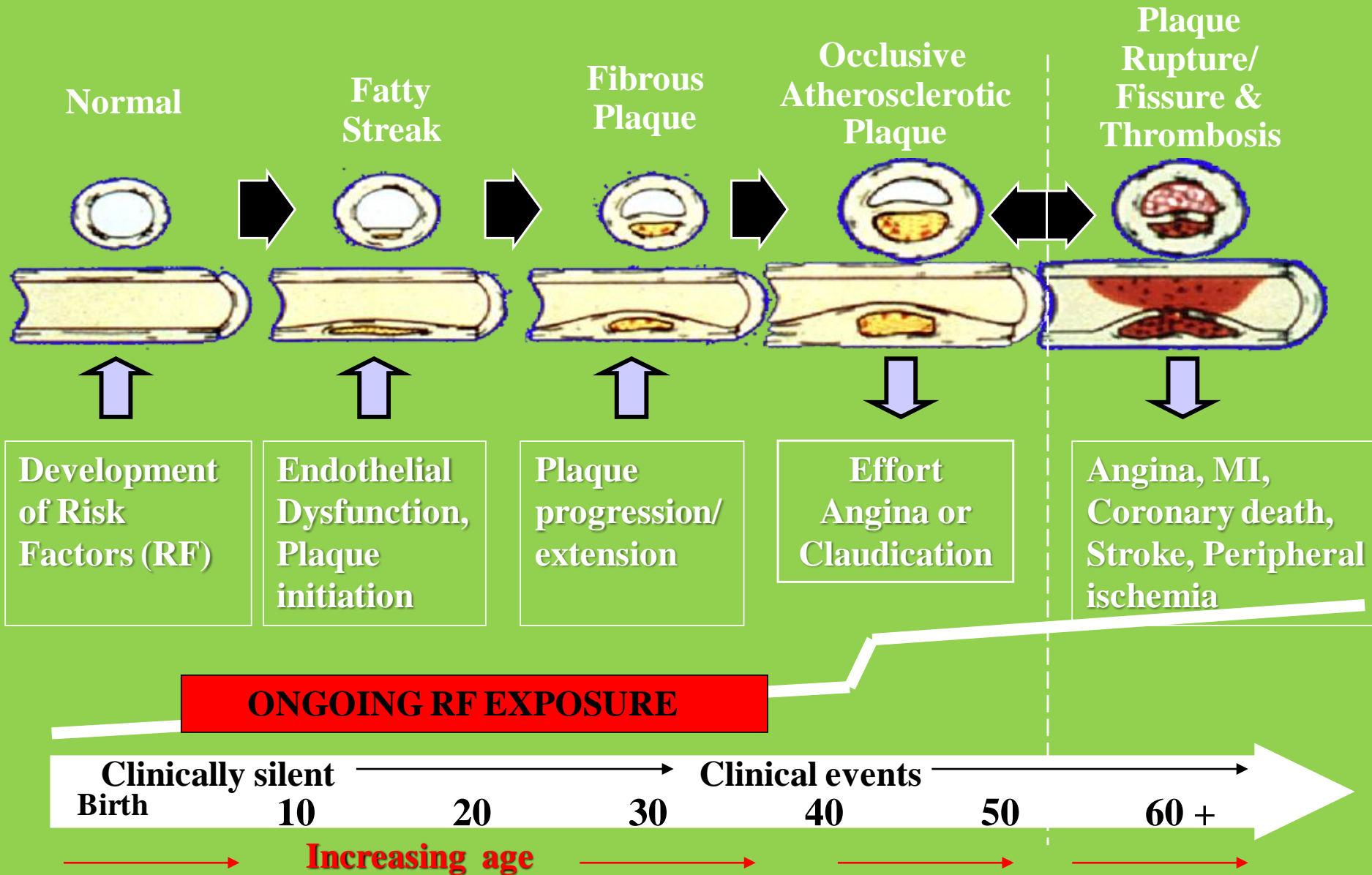
Metabolic Risk for Cardiovascular Disease American Heart Association Clinical Series



Body Mass Index and Diabetes Risk



Atherosclerosis: A Progressive Process



Childhood Obesity

- ~17% (or 12.7 million) of children and adolescents aged 2—19 years are obese
 - BMI \geq 95%
 - Among children aged 2 to 5 years decreased significantly from 13.9% in 2003-2004 to 8.4% in 2011-2012.
- Obesity more common among certain racial and ethnic groups (2011-2012)
 - Hispanics (22.4%)
 - Non-Hispanic blacks (20.2%)
 - Non-Hispanic whites (14.1%)
 - Non-Hispanic Asian youth (8.6%)



Antipsychotic Use in Youth

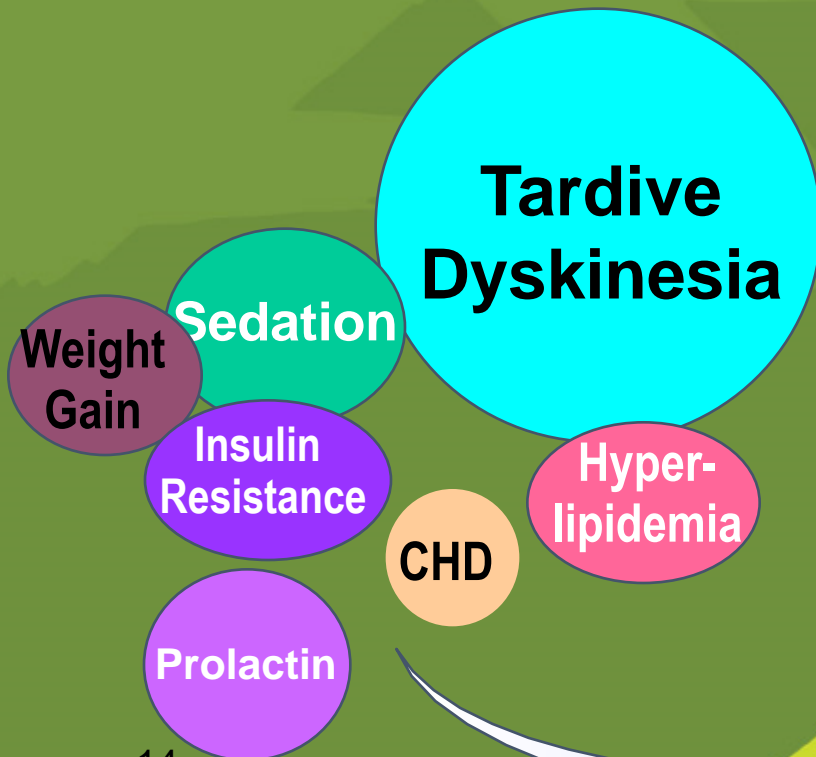
- First line treatment for Schizophrenia Spectrum Disorders
 - Used in conjunction with psychotherapeutic interventions
- Second generation agents generally preferred
 - Risperidone
 - Olanzapine
 - Aripiprazole
 - Quetiapine
 - Paliperidone
- Treatment of Early Onset Schizophrenia Study (TEOSS)
 - Symptom improvement in responders plateau after 8 weeks
 - Few completed 12 months of therapy on original medication

AACAP Practice Parameter Schizophrenia 2013

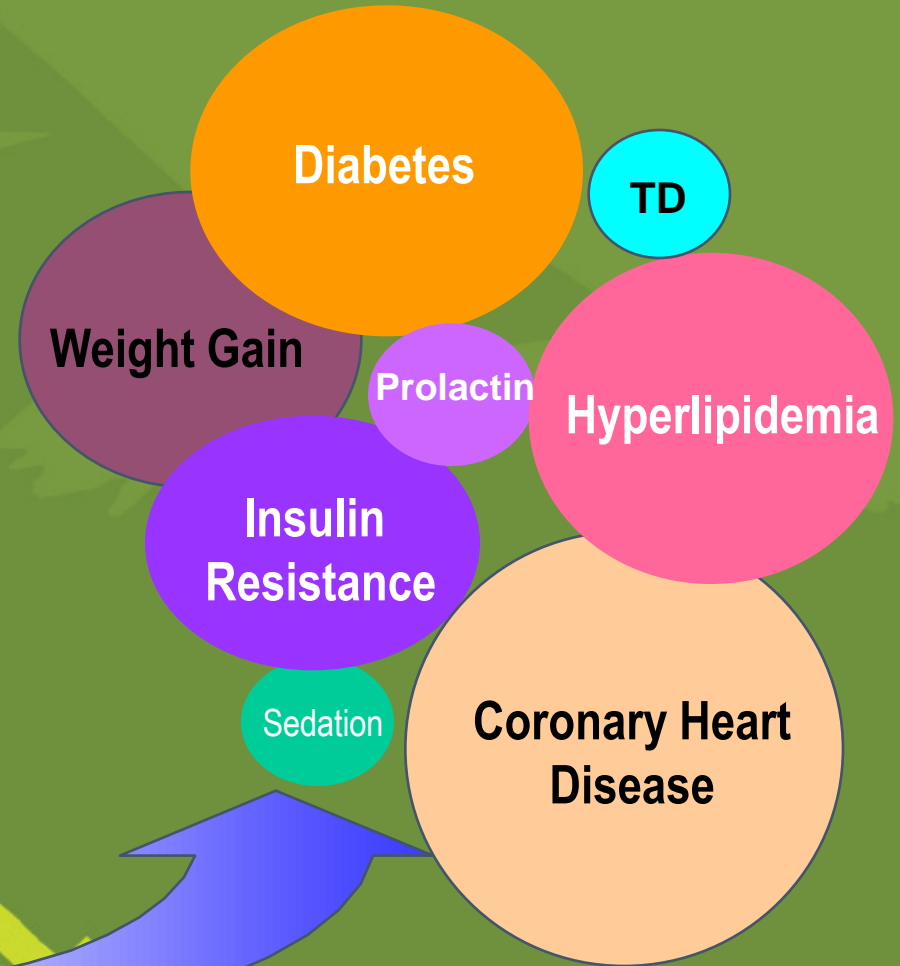


Shift in Risk Perception of Antipsychotics

Past Areas of Concern



Current Medical Realities



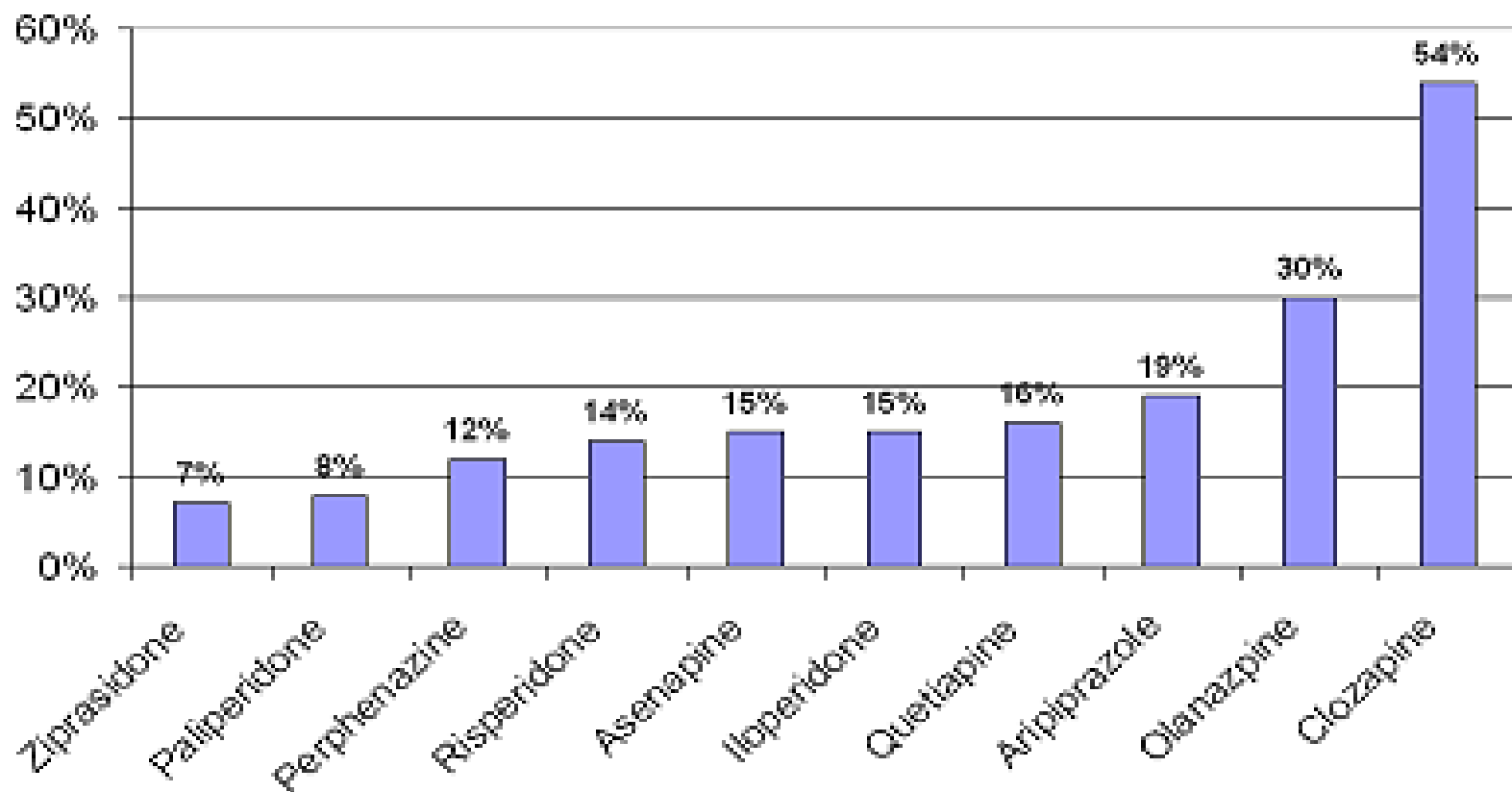
Modifiable Risk Factors Affected by Antipsychotic Medication

- Overweight / Obesity
- Insulin resistance
- Diabetes/hyperglycaemia
- Dyslipidemia



Antipsychotic Associated Weight Gain

Patients with greater than 7% weight gain



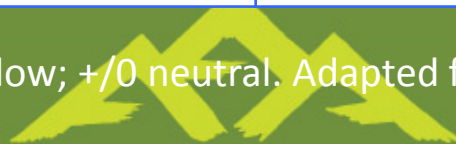
Adapted from Efficacy of Metformin and Topiramate in Prevention and Treatment of Second-Generation Antipsychotic-Induced Weight Gain. *The Annals of Pharmacotherapy* 2010;44:668-679



Atypical Antipsychotics: Metabolic Concerns

Drug	Weight gain	Hyperglycemia	Dyslipidemia
Clozapine	+++	+++	+++
Olanzapine	+++	+++	+++
Risperidone	++	+	+
Paliperidone	+	+	+
Quetiapine	++	++	++
Iloperidone	++	+/0	+/0
Ziprasidone	+/0	+/0	+/0
Aripiprazole	+/0	+/0	+/0
Asenapine	+/0	+/0	+/0
Lurasidone	+/0	+/0	+/0
Cariprazine	+/0	+/0	+/0
Brexipiprazole	+/0	+/0	+/0

NOTES: +++ significant, ++ moderate; + low; +/0 neutral. Adapted from *Current Psychiatry* 2013;12(9):51-54.



Metabolic Adverse Effects in Youth

- Naturalistic study, youth (4-19 years) naive to antipsychotic therapy. ~3months of treatment
- Weight Gain (percent gaining >7%)
 - 4.4 kg on aripiprazole (58.4%)
 - 5.3 kg on risperidone, (64.4%)
 - 6.1 kg on quetiapine, (55.6%)
 - 8.5 kg on olanzapine (84.4%)
- Increased fat mass, waist , BMI
 - 36.1% shifted to overweight or obese
- Glucose and lipid changes, except aripiprazole



EUFEST: First Episode Schizophrenia

Weight Changes with Treatment

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone
Overweight (BMI ≥ 25 kg/m ²)	16/43 (37%)	31/72 (43%)	45/83 (54%)	25/55 (45%)	14/43 (33%)
Weight gain >7% from baseline	23/43 (53%)	45/72 (63%)	71/83 (86%)	36/55 (65%)	16/43 (37%)
Weight change from baseline (kg)	7.3 (1.8)	9.7 (1.7)	13.9 (1.7)	10.5 (1.8)	4.8 (1.9)



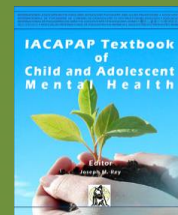
Side Effects of Antipsychotic Medications

Weight Gain

- Most common long term adverse effect of atypicals
- 5% weight gain in 1st 3 months or 0.5 increase in BMI concerning
- Dyslipidemia, metabolic syndrome, diabetes mellitus, hypertension, polycystic ovary,
- Social withdrawal, treatment discontinuation, self esteem

Metabolic Syndrome

- Obesity, hypertriglyceridemia, low HDL, hypertension, hyperglycemia
- Precursor = weight gain
- Insulin secretion problems
- Especially clozapine and olanzapine



Traditional Mood Stabilizers: What are examples of these?

- Lamotrigine (Lamictal)
- Lithium (Lithobid)
- Valproic acid derivatives (Depakote, Depakene)
- Carbamazepine (Tegretol)
- Oxcarbamazepine (Trileptal)

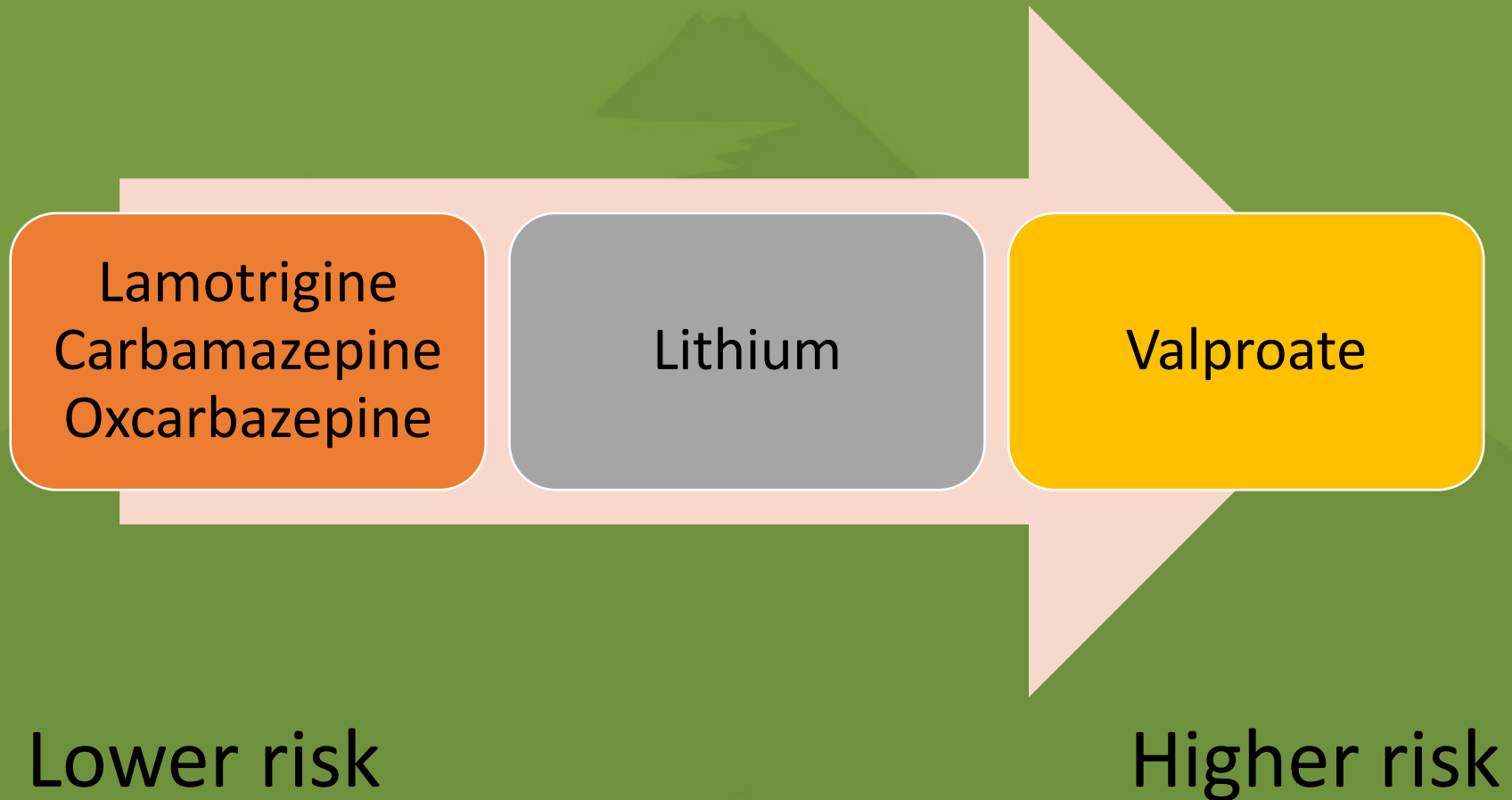


Traditional Mood Stabilizers: Why are they prescribed?

- Seizures
- Mood
 - Major depressive disorder
 - Bipolar disorder
 - Schizoaffective disorder
- Pain/neuropathy
- Migraine prevention
- Alcohol detoxification



Traditional Mood Stabilizers: What is their metabolic risk?



Traditional Mood Stabilizers: What is their metabolic risk?

- Poorly understand and variable reports
- Valproate associated weight gain may be related to
 - Increased appetite and carbohydrate craving
 - Increased thirst (may drink high calorie fluids to quench)
 - Increased insulin which can lead to insulin resistance and metabolic syndrome
 - Average weight gain ~10lb; significant weight gain 1 in 5 patients
- Lithium associated weight gain may be related to
 - Decreased thyroid function which slows body's metabolism
 - Direct appetite stimulation
 - Body holds onto fluids more (fluid retention)
 - Increased thirst
 - Average weight gain ~5-10lb; significant weight gain 3 in 10 patients



Antidepressants: What are examples of these?

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Fluoxetine (Prozac)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)*
- Sertraline (Zoloft)

Selective Norepinephrine Reuptake Inhibitors (SNRIs)

- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)
- Levomilnacipran (Fetzima)
- Venlafaxine (Effexor)

* = higher metabolic risk within the class



Antidepressants: What are examples of these?

Tricyclic Antidepressants (TCAs)

- Tertiary TCAs*
 - Amitriptyline (Elavil)*
 - Imipramine (Tofranil)
 - Doxepine (Silenor)
- Secondary TCAs
 - Nortriptyline (Pamelor)
 - Desipramine (Norpramin)

Monoamine Oxidase Inhibitors (MAOIs)

- Phenzelzine (Nardil)*
- Selegiline (Eldepryl, Emsam)
- Tranylcypamine (Parnate)

* = higher metabolic risk within the class



Antidepressants: What are examples of these?

Atypical Antidepressants

- Mirtazapine (Remeron)*
- Bupropion (Wellbutrin)
- Trazodone (Oleptro)
- Nefazodone (Serzone)

Newer Antidepressants

- Vilazodone (Viibryd)
- Vortioxetine (Brintellix, Trintellix)

* = higher metabolic risk within the class

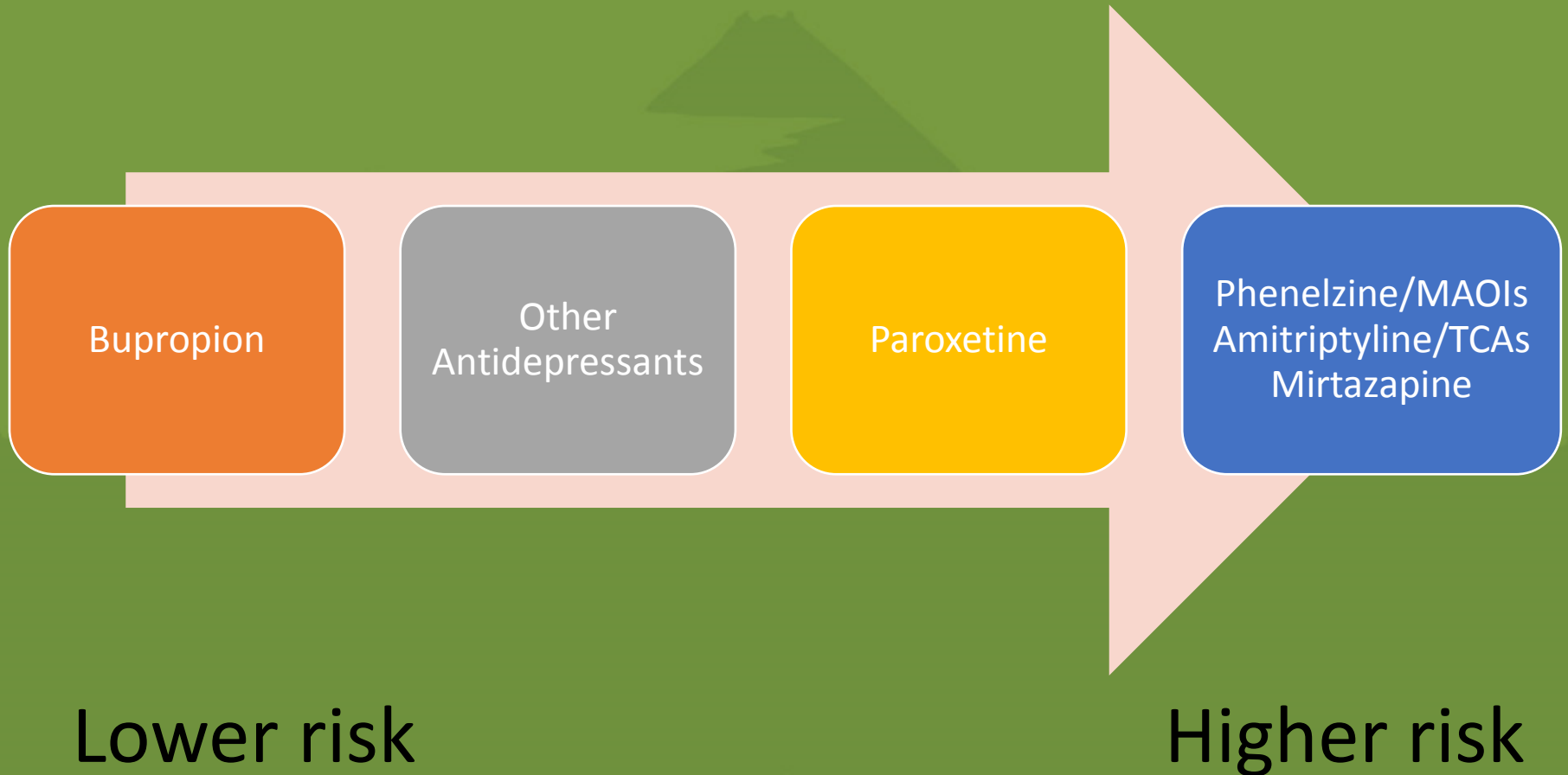


Antidepressants: Why are they prescribed?

- Anxiety
- Mood
- Insomnia
- Pain/neuropathy
- Fibromyalgia
- Migraine prevention
- Eating disorders
- Attention Deficit Hyperactivity Disorder
- Irritable bowel syndrome



Antidepressants: What is their metabolic risk?



Antidepressants: What is their metabolic risk?

- MAOIs and TCAs are MORE likely to cause weight gain in the short and long-term compared to other antidepressants
- Mirtazapine likely presents at least similar weight gain risk as TCAs but may also cause lipid (fat) abnormalities
- SSRIs may be MORE likely to cause weight gain in the long-term (>1 year) vs. short-term; this is controversial
- Paroxetine may be MORE likely than other SSRIs to cause weight gain
- Nefazodone and venlafaxine are likely to have no effect on weight vs. SSRIs or TCAs
- Bupropion is likely to cause weight loss



Medication	Average weight gain (lbs) in short-term (<12 weeks)	Average weight gain (lbs) in long-term (>4 months)
Bupropion	↓ 2.5	↓ 3-4
Buspirone	None ^a	None ^a
Citalopram	↓ 1-2	↑ 3.5
Desvenlafaxine	↓ 1-2	↓ 1-2
Duloxetine	↓ 1-2	↑ 1-2
Escitalopram	↓ < 1	↑ 1-2
Fluoxetine	↓ 1-2	↓ < 1
Fluvoxamine	↓ < 1	Limited data ^a
Mirtazapine	↑ 3.5	↑ 5
Nefazodone	Minor changes ^a	None ^a
Paroxetine	↓ < 1	↑ 5
Sertraline	↓ 1-2	↓ < 1
Venlafaxine	↓ < 1	Minor changes ^a
Vilazodone	Minor changes ^a	↑ 3 ^a

^aBased on limited data



Minimizing Metabolic Risk

Achieve illness
remission and
recovery

Monitor for
risk

Adopt
Lifestyle
Changes

Medication
Management



Monitoring for Metabolic Risk: What may we monitor?

- Personal and family history
- Weight/body mass index (BMI)/waist circumference
- Blood pressure
- Hemoglobin A1c
 - Measures average blood sugar over 3 month period
 - May not be accurate measure in patients with renal disease, liver disease, or with conditions that effect hemoglobin
- Lipid panel
 - Measures different fats in the blood
 - Limited use during pregnancy and eating disorders



Monitoring for Metabolic Risk: When do we monitor?

Table 1. Recommended monitoring when starting an atypical antipsychotic.

Measurement	Baseline	4 weeks	8 weeks	12 weeks	Yearly
Medical History	+				
Weight/BMI/ waist ^a	+	+	+	+	+
Blood Pressure	+	+/-	+/-	+	+
Lipid Panel	+		+/-	+	+
Fasting Plasma Glucose (FPG)/ HgbA1c ^b	+		+/-	+	+
Lifestyle Advice	+	+	+	+	+

^a = Patients should self-monitor as well

^b = Unless patient develops diabetes in which case American Diabetes Association guidelines are recommended

+ = monitor

+/- = mixed recommendations



Monitoring for Metabolic Risk: When do we monitor?

- “On demand” testing if clinically warranted
 - Symptoms of pancreatitis, heart attack, or stroke
 - Symptoms of high blood glucose (increased thirst and urination, weakness, unintentional weight loss)
- Monitoring for typical antipsychotics often follows monitoring for atypical antipsychotics (see last slide)
- Monitoring for traditional mood stabilizers and antidepressants varies but is mainly limited to weight/BMI and blood pressure
 - Good practice to obtain weight and blood pressure at every office
 - A1c and lipid panel will be obtained as clinical symptoms warrant or guideline recommendations



Monitoring for Metabolic Risk: When should we be concerned?

- Providers look at trends and abnormal values
- Weight gain $\geq 7\%$ body weight or increasing BMI categories
- Waist circumference >35 -in (women) or >40 -in (men)
- Blood Pressure $> 140/90$ mmHg
- Abnormal lipids
 - Triglycerides > 500 requires specific intervention
- Development of diabetes mellitus
 - A1c $\geq 6.5\%$, FPG ≥ 126 mg/dL, random blood glucose ≥ 200 mg/dL WITH symptoms
- Development of prediabetes
 - A1c 5.7 – 6.4% or FPG 120-125 mg/dL

FPG = fasting plasma glucose



Minimizing Metabolic Risk: Positive Lifestyle Habits

Positive Habits

- Control calorie intake
- Eat a balanced diet
- Increase activity
- Achieve restful sleep
- Decrease stress
- Minimize alcohol use
- Stop smoking

Implementation Ideas

- Limit soda, sports drinks, and juice
- Gradually decrease portion sizes
- Eat smaller but more frequent meals
- Limit “screen time” to < 2 hours daily
- Use a pedometer/fitbit



Minimizing Metabolic Risk: Medication Management Overview

Strategy	Advantages	Disadvantages
Use non-drug interventions	Can continue current meds Can avoid adding another med General health benefits	General lack of acceptance May not be enough
Avoid higher risk meds	Likely beneficial	Limits medication options
Switch meds to one with lower risk	Likely beneficial	Possible that illness will worsen or reoccur
Add-on therapy	Can continue current meds	May not be beneficial Can increase side effect burden Can cause drug interactions Added cost



Minimizing Metabolic Risk: Add on therapy

- If other strategies have failed or pose too many risks, add-on therapy may be considered
- This strategy treats a drug side effect with another drug
- Most studies focus on managing antipsychotic or mood stabilizer associated weight gain using metformin (750-2550 mg/d) or topiramate (100-250 mg/d) for < 3-6 months in ADULT patients
 - Metformin side effects = stomach discomfort, loose stools
 - Topiramate side effects = drowsiness, memory problems, kidney stones, tingling, nearsightedness
 - Weight loss ~5-6 lb



Advocacy

- Do NOT stop taking your medications if you have concerns over metabolic risk
 - Abruptly stopping medications poses serious risk!
- Discuss with your healthcare providers
 - “How are you going to monitor risk associated with starting or continuing my medications?”
 - “I would like to follow and understand my lab results.”
 - “I am concerned my medications may be doing more harm than good.”
 - “I am not following your explanation. Would you please explain it to me another way?”
 - “Would you provide resources so I can learn more about risks and management?”



Resources

- Ask if you have pharmacist as part of your healthcare team to discuss medication concerns
 - If not, speak to pharmacists available in the community about your risk and how to best monitor and manage
- Other community resources
 - www.getoutdoorscolorado.org
 - www.hungerfreecolorado.org



THE RELATIONSHIP BETWEEN INDIVIDUALS WITH MENTAL HEALTH CONDITIONS AND COMMUNITY PHARMACISTS

- 91% of individuals taking mental health medication are very comfortable going to community pharmacies, and 83% report feeling respected by their pharmacist
- 53% of individuals taking mental health medications have a strong professional relationship with their pharmacist, 43% report that they do not have such a relationship
- *75% of individual respondents reported that they did not receive effectiveness or safety monitoring assistance from their pharmacist*
- The primary concern from individuals taking mental health medications is a lack of privacy (58%), with no available space for private conversations with their pharmacist being one of the most frequently reported obstacles



National Alliance on Mental Illness



Denver, July



Resources

- Mobile Health Applications
 - Lose It
 - Weight watchers mobile
 - Diet Assistant
 - MyFitnessPal
 - Fitocracy
 - Ideal Weight
 - Weight Loss Coach by Fooducate
- Activity Trackers
- Programs:
 - Weight Watchers
 - MOVE (www.move.va.gov)
 - American Diabetes Association: www.diabetes.org/living-with-diabetes.
- Medication Information (NAMI Med Sheets)



Select References

- American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care*. 2016;39(Suppl 1).
- De Hert M, Vancampfort D, Correll CU, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: a systematic evaluation. *B J Psych*. 2011;199(2):99-105.
- Deshmukh R and Franco K. Managing weight gain as a side effect of antidepressant therapy. *Cleve Clin J Med*. 2003;70(7):614, 616, 618, passim.
- Hasnain M and Vieweg WV. Weight considerations in psychotropic drug prescribing and switching. *Postgrad Med*. 2013;125(5):117-29.
- Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry*. 2010;71(10):1259-1272.
- Zeier K, Connell R, Resch W, et al. Recommendations for lab monitoring of atypical antipsychotics. *Current Psychiatry*. 2013;12(9):51-54.
- Meyer JM, Nasrallah H, McEvoy JP, et al. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial: Clinical Comparison of subgroups with and without metabolic syndrome. *Schiz Research*. 2005;80:19-32
- Colditz GA et al. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med*. 1995;122:481
- Correll CU, Manu P, Olshankiy V et al. Cardiometabolic Risk of Second-Generation Antipsychotic Medications During First-Time Use in Children and Adolescents. *JAMA*. 2009;302(16):1765-1773



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