Metabolic Effects of Psychiatric Medications and HIV Medications

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Sept 29, 2021

Learning Objectives

- Review relative effects of psychiatric medications on weight
- Understand psychotropic medications which may worsen risk for metabolic effects, insulin resistance and diabetes
- Review the effect of HIV medications on insulin resistance and lipodystrophy
- Review limited literature on medications that may have metabolic benefit

Disclosures:

- Dr. Ehrhardt has received a consulting fee from Novo Nordisk and received investigator initiated grants from Dexcom and educational grants for Merck and Novo Nordisk

Psychotropic Medication Classes Depression/Anxiety

- **Selective Serotonin Reuptake Inhibitors (SSRI)**

-Citalopram(celexa), fluoxetine (Prozac), sertraline (Zoloft) , paroxetine (paxil,) escitalopram(Lexapro)

- **Serotonin Norepinephrine Reuptake Inhibitors (SNRI)**

-Venlafaxine (Effexor™) Duloxetine (Cymbalta™), Desvenlafaxine (Pristique™)

- **Tricyclic Antidepressants**:

- amitriptyline, nortriptyline

- 5-Hydroxytryptamine **(5-HT2) Antagonists**

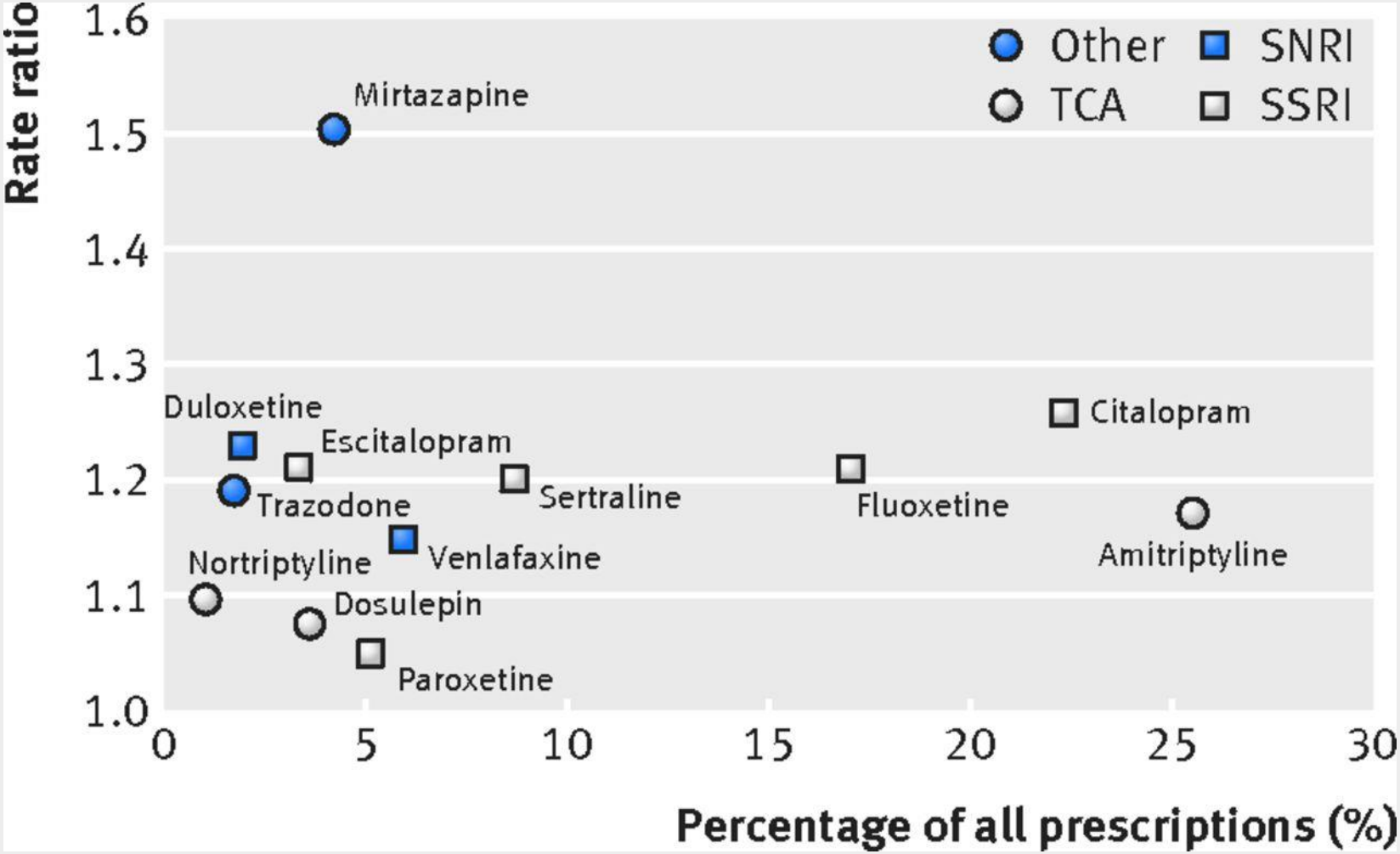
-Mirtazapine(remeron) and trazodone

Weight Gain from Anti-depression Medications vs from Depression

- Effect on metabolism and hunger
- Depression itself may cause weight gain in some people and weight loss in others
- Antidepressants interfere with serotonin, the neurotransmitter that regulates anxiety and also appetite
- In Depression: lack of physical activity can cause weight gain

Shi Z et al. BMJ Open. 2017 Aug 11;7(8):e016224

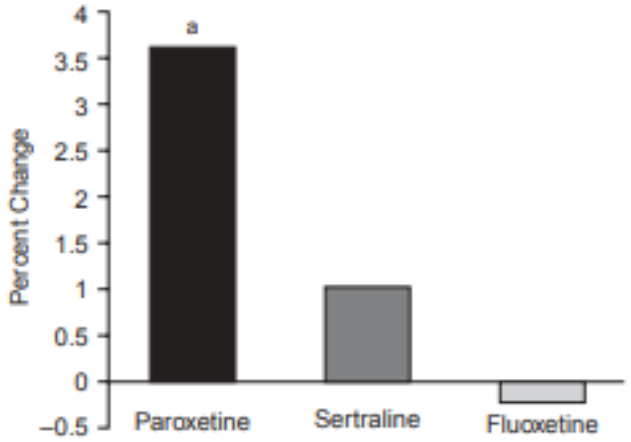
Scatter plot of adjusted rate ratios for ≥5% weight gain by number of prescriptions.



Rafael Gafoor et al. BMJ 2018;361:bmj.k1951

Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment

Figure 1. Mean Percent Change in Weight From Baseline to Endpoint After 26 to 32 Weeks of Therapy



[a]Significant difference within paroxetine group compared with baseline ($t = 3.92$, $df = 46$, $p < .001$), and for paroxetine vs. sertraline ($t = 2.46$, $df = 136$, $p = .015$) and paroxetine vs. fluoxetine ($t = -3.55$, $df = 136$, $p < .001$) at endpoint.

Fava et al. J Clin Psychiatry. 2000 Nov;61(11):863-7.

Weight Change over 2 years for Anti-Depression Medications

Table 2

Estimated 2-year weight change (lbs) for users of the various drug groups compared to fluoxetine users based on the intent-to-treat analysis *.

	Unweighted Estimates			Weighted Estimates		
	Estimate	*p*-Value	95% CI	Estimate	*p*-Value	95% CI
Bupropion-non smoker	−7.6	<0.01	(−11.5, −3.7)	−7.1	<0.01	(−11.3, −2.8)
Bupropion-smoker	1.0	0.65	(−3.2, 5.2)	2.2	0.33	(−2.3, 6.8)
Citalopram	0.3	0.82	(−2.3, 2.9)	1.2	0.40	(−1.6, 4.1)
Duloxetine	−0.6	0.91	(−11.4, 10.1)	−1.0	0.88	(−13.5, 11.5)
Mirtazapine	12.7	0.08	(−1.5, 27.0)	11.6	0.12	(−2.8, 26.0)
Paroxetine	−0.5	0.84	(−5.7, 4.7)	0.8	0.78	(−5.0, 6.6)
Sertraline	3.3	0.15	(−1.2, 7.9)	5.9	0.02	(0.8, 10.9)
Trazodone	0.4	0.84	(−3.9, 4.8)	0.8	0.75	(−3.9, 5.5)
Venlafaxine	−6.7	0.14	(−15.5, 2.1)	−2.0	0.67	(−11.3, 7.3)

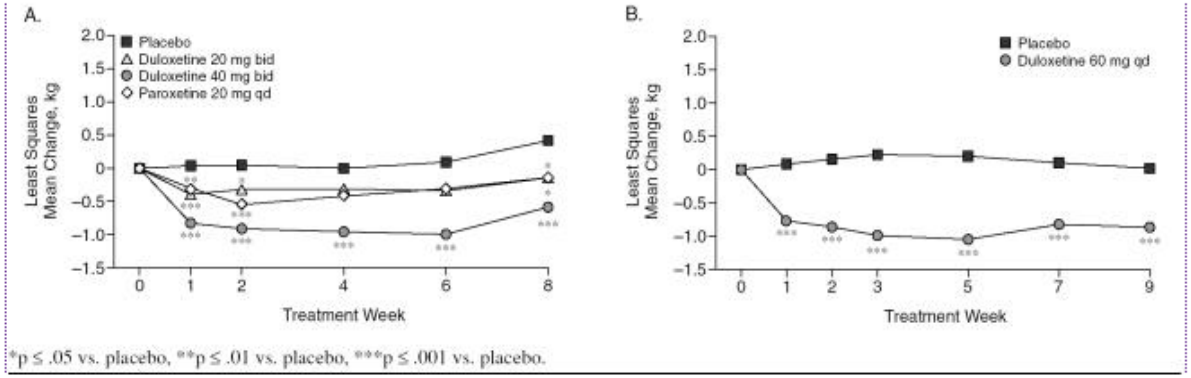
* Results in the left part of the table refer to the unweighted modelling that ignores selection bias, while the right side of the tables provides the inverse probability weighted (IPW) estimation results. Omnibus *p*-values for the null hypothesis "all drugs have the same effect on weight change" were 0.004 (naive analysis) and 0.009 (IPW analysis). Analyses were adjusted for age, gender, baseline weight, smoking status, and active psychotherapy.

Arterburn D et al. *J Clin Med*. 2016;5(4):48. Published 2016 Apr 13.

Effects of the Antidepressant Duloxetine on Body Weight: Analyses of 10 Clinical Studies

- In a 52-week open-label study, patients had a mean weight gain of 1.1 kg ($p < .001$).

Figure 1.



Change in Body Weight During (A) 8 Weeks of Acute Treatment With Duloxetine 40 mg/day (20 mg b.i.d.), Duloxetine 80 mg/day (40 mg b.i.d.), Paroxetine 20 mg/day (20 mg q.d.), or Placebo (studies 3 and 4; repeated measures analysis) and (B) 9 Weeks of Acute Treatment With Duloxetine 60 mg/day (60 mg q.d.) or Placebo (studies 7 and 8; repeated measures analysis)

Wise TN et al. Prim Care Companion J Clin Psychiatry. 2006;8(5):269-278.

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TABLE 1

Effect of antidepressant drugs on body weight

DRUG	EFFECT ON WEIGHT
Monoamine oxidase inhibitors (irreversible type)	Weight gain likely in short term (< 6 months) and long term (≥1 year)
Tricyclic compounds	Weight gain likely in short term and long term
Selective serotonin reuptake inhibitors (SSRIs) other than paroxetine	Weight gain in short term less likely Weight gain in long term possible, but evidence is varied
Paroxetine	Weight gain in short and long term more likely than for other SSRIs
Nefazodone	Likely to have no effect on weight
Bupropion	Likely to cause weight loss
Mirtazapine	More likely than placebo to cause weight gain in short term, but less likely than tricyclics
Venlafaxine	Likely to have no effect on weight

Deshmukh et al. Cleve Clin J Med. 2003 Jul;70(7):614.

Weight loss & More Weight Neutral/Less Gain

- Bupropion (Aplenzin, Forfivo, Wellbutrin)
- Duloxetine (Cymbalta)
- Selegiline (Emsam) (transdermal and a monoamine oxidase inhibitor (MAOI))

https://www.medicalnewstoday.com/articles/319527#other-types-of-antidepressants

- Idesvenlafaxine (Pristiq)
- escitalopram (Cipralex, Lexapro)
- levomilnacipran (Fetzima)
- nefazodone (Serzone)
- venlafaxine (Effexor)
- venlafaxine ER (Effexor XR)
- vilazodone (Viibryd)
- vortioxetine (Trintellix)

- If used on a short-term basis of fewer than 6 months
- citalopram (Celexa)
- fluoxetine (Prozac)
- sertraline (Zoloft)

Mood Stabilizers

- **Mood stabilizers** used to treat bipolar disorder
- Lithium (Lithobid), valproic acid (Depakene), divalproex sodium (Depakote), carbamazepine (Tegretol, Equetro) and lamotrigine (Lamictal).
- All of these medications are known to increase the risk of weight gain except lamotrigine

Kemp DE. J Affect Disord. 2014 Dec;169 Suppl 1:S34-44
Hasnain M, et al.Postgraduate Medicine. 2013;125:117.
https://www.mayoclinic.org/diseases-conditions/bipolar-disorder/expert-answers/bipolar-medications-and-weight-gain/faq-20058043

Antipsychotics

- Most **antipsychotics** are **dopamine** antagonists

-Treat: schizophrenia, bipolar disorder, and stimulant psychosis

- Dopamine receptor antagonists (DRA) : First Generation "typical":

- Serotonin Dopamine Antagonists (SDA): Second Generation Antipsychotics "atypical"

https://psychopharmacologyinstitute.com/antipsychotics-videos/first-second-generation-antipsychotics/

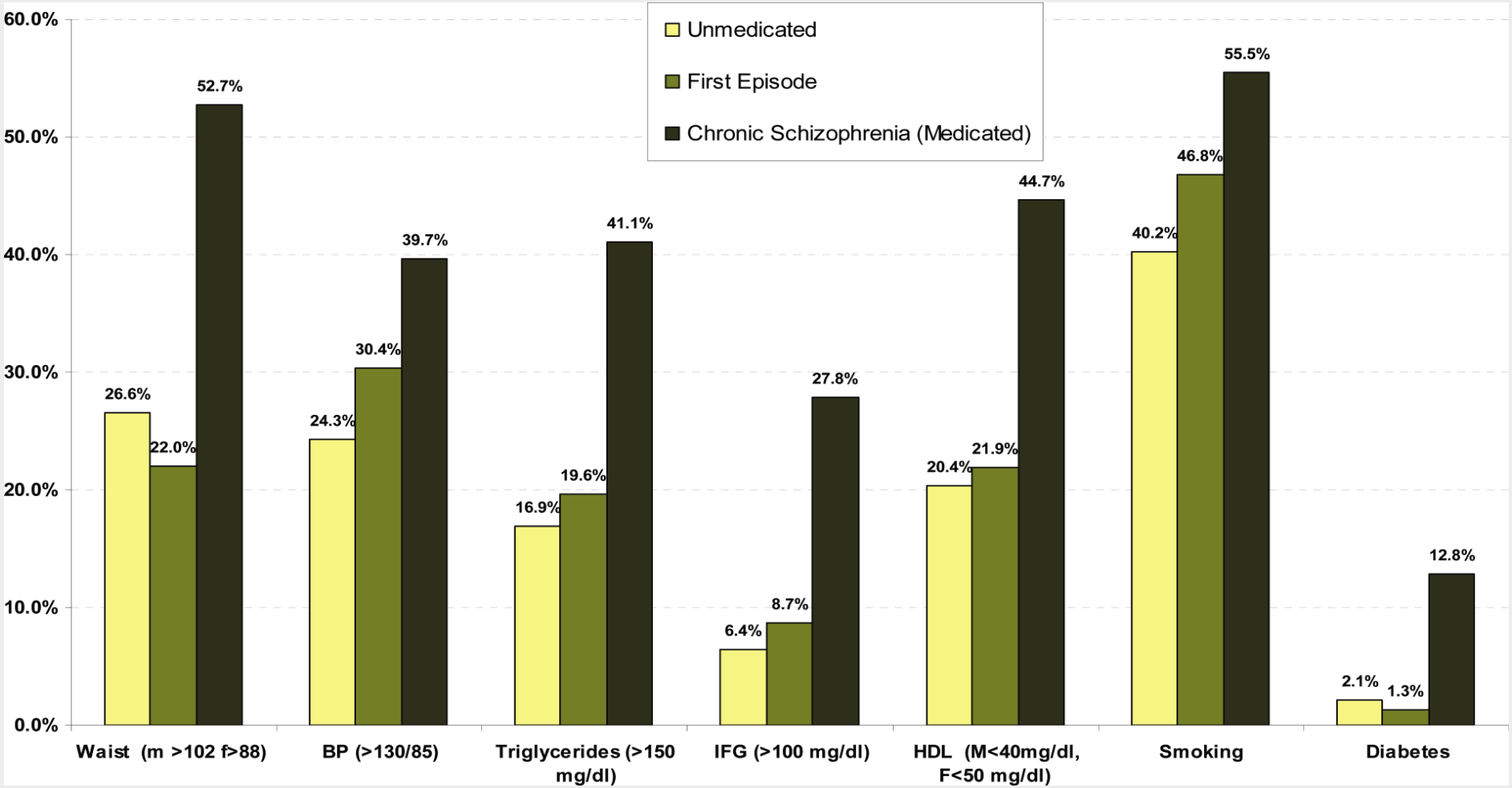
List of Antipsychotics

First-Generation Antipsychotics	Second-Generation Antipsychotics
•Chlorpromazine •Droperidol •Fluphenazine •Haloperidol •Loxapine •Perphenazine •Pimozide •Prochlorperazine •Thioridazine •Thiothixene •Trifluoperazine	**Monotherapy** •Aripiprazole-3rd •Asenapine •Clozapine •Iloperidone •Lurasidone •Olanzapine •Paliperidone •Quetiapine •Risperidone •Ziprasidone **Combination therapy** •Olanzapine plus fluoxetine

Adverse effects profile

First Generation Antipsychotics	Second Generation Antipsychotics
• Higher risk of neurological side effects	• Higher risk of metabolic side effects

Schizophrenia, Medications, and Metabolic Syndrome Components



Mitchell AJ et al . Schizophr Bull. 2013 Mar;39(2):295-305

Atypical Anti-Psychotic

- Atypical antipsychotic medications can cause weight gain, glucose dysregulation, diabetes, and dyslipidemia
- Bind to non-dopaminergic targets, including serotonin, glutamate, histamine, alpha-adrenergic, and muscarinic receptors
- Olanzapine, followed by zotepine and clozapine were associated the highest risk for weight gain
- Quetiapine, risperidone, and paliperidone- some risk
- Haloperidol, and ziprasidone and lurasidone had risk of weight gain no different from placebo

Leucht, S. et al. Lancet 382, 951–962 (2013)

Comparison of Atypical Antipsychotics

- Olanzapine and quetiapine: largest mean increase in waist circumference, then risperidone
- No changes for ziprasidone and a decrease in waist circumference for perphenazine
- Substantially greater weight gain with olanzapine (0.9 kg/month) vs. quetiapine or risperidone (both 0.2 kg/month)
- Perphenazine and ziprasidone were associated with losses of 0.1 kg/month

Lieberman JA et al. N Engl J Med. 2005; 353: 1209–1223 Erratum in N Engl J Med. 2010; 363: 1092–1093

Initiating Anti-Psychotics

TABLE 1. After baseline metabolic parameters are obtained, suggested frequency of metabolic monitoring for patients who take antipsychotic medications[a]

Parameter	Adult patients	Pediatric patients[b]
Personal and family history[c]	Annually	Annually
Lifestyle behaviors[d]	N/A	Each visit
Height, weight, BMI	Every 4 weeks for the first 12 weeks, then every 3 months	Each visit
Waist circumference	Annually	N/A
Blood pressure, pulse; fasting blood glucose; lipids	12 weeks, then annually	3 months, then every 6 months
Electrocardiography	Not specified	N/A

[a] May be conducted more frequently, as indicated.
[b] Other parameters, including thyroid-stimulating hormone, prolactin, and sexual/reproductive dysfunction are also recommended in pediatric patients.
[c] For example, obesity, diabetes, dyslipidemia, hypertension, coronary heart disease.
[d] For example, exercise, diet, smoking.
N/A, not available; the guidelines do not specifically address these items.

Diabetes Care 2004 Feb; 27(2): 596-601.

Bostwick et al. Psychiatric Times, Vol 34 No 5.

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

Table 2—*SGA's and metabolic abnormalities*

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/−	−	−
Ziprasidone*	+/−	−	−

+ = increase effect; − = no effect; D = discrepant results. *Newer drugs with limited long-term data.

Diabetes Care 2004 Feb; 27(2): 596-601.

Atypical

- Consider transitioning to those with less weight gain or dyslipidemia potential is seeing metabolic effects
- Aripiprazole, ziprasidone, lurasidone and cariprazine more weight neutral but varies by pt
- Example case report of two people with bipolar who gained weight on Aripiprazole

Singh T. *Psychiatry (Edgmont)*. 2005;2(6):19.

Question: A young man with newly diagnosed schizophrenia gains weight after starting treatment. Which medication is most likely at play?

1. Aripiprazole (Abilify)
2. Risperidone (Risperdal)
3. Ziprasidone (Geodon)
4. Olanzapine (Zyprexa)

Question: A middle aged woman taking medication for depression loses several pounds over a year. Which medication is most likely at play?

1. Paroxetine (Paxil)
2. Bupropion (Wellbutrin)
3. Mirtazapine (Remeron)
4. Sertraline (Zoloft)

Psychotropic Medications and Weight

- Gain:
  - Olanzapine: 2.4kg
  - Gabapentin: 2.2kg
  - Amitriptyline: 1.8kg
  - Mirtazapine: 1.5kg
  - Quetiapine: 1.1kg
- Loss:
  - Topiramate: 3.8kg
  - Bupropion: 1.3kg

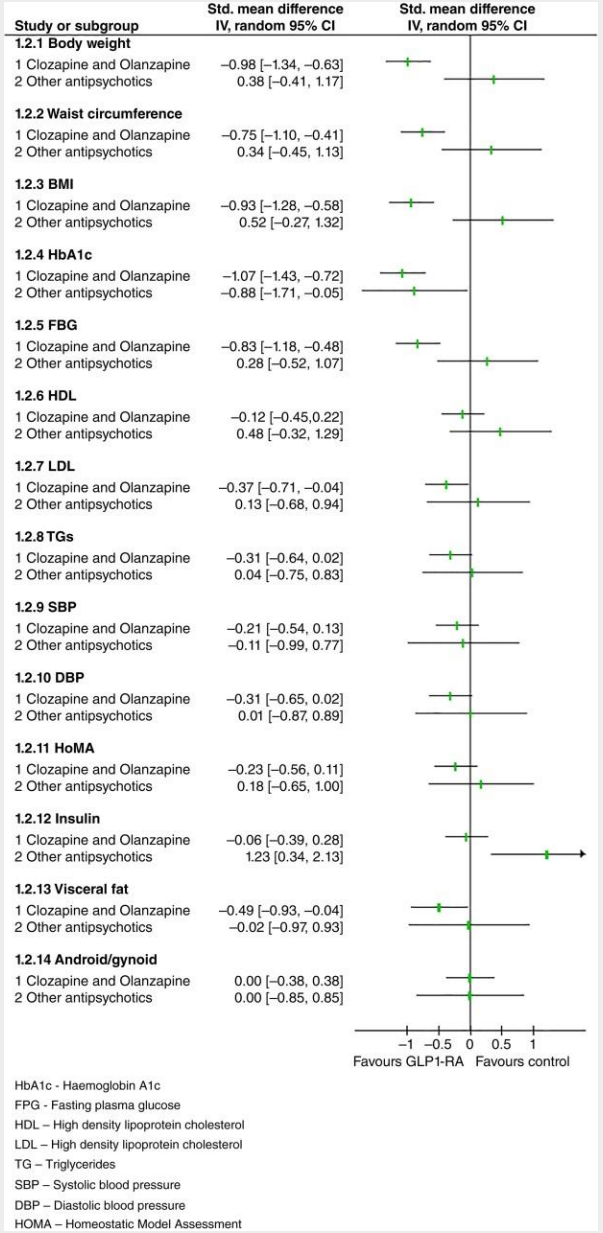
Domecq JP et al. J Clin Endocrinol Metab. 2015 Feb;100(2):363-70

Attenuation of Weight Gain

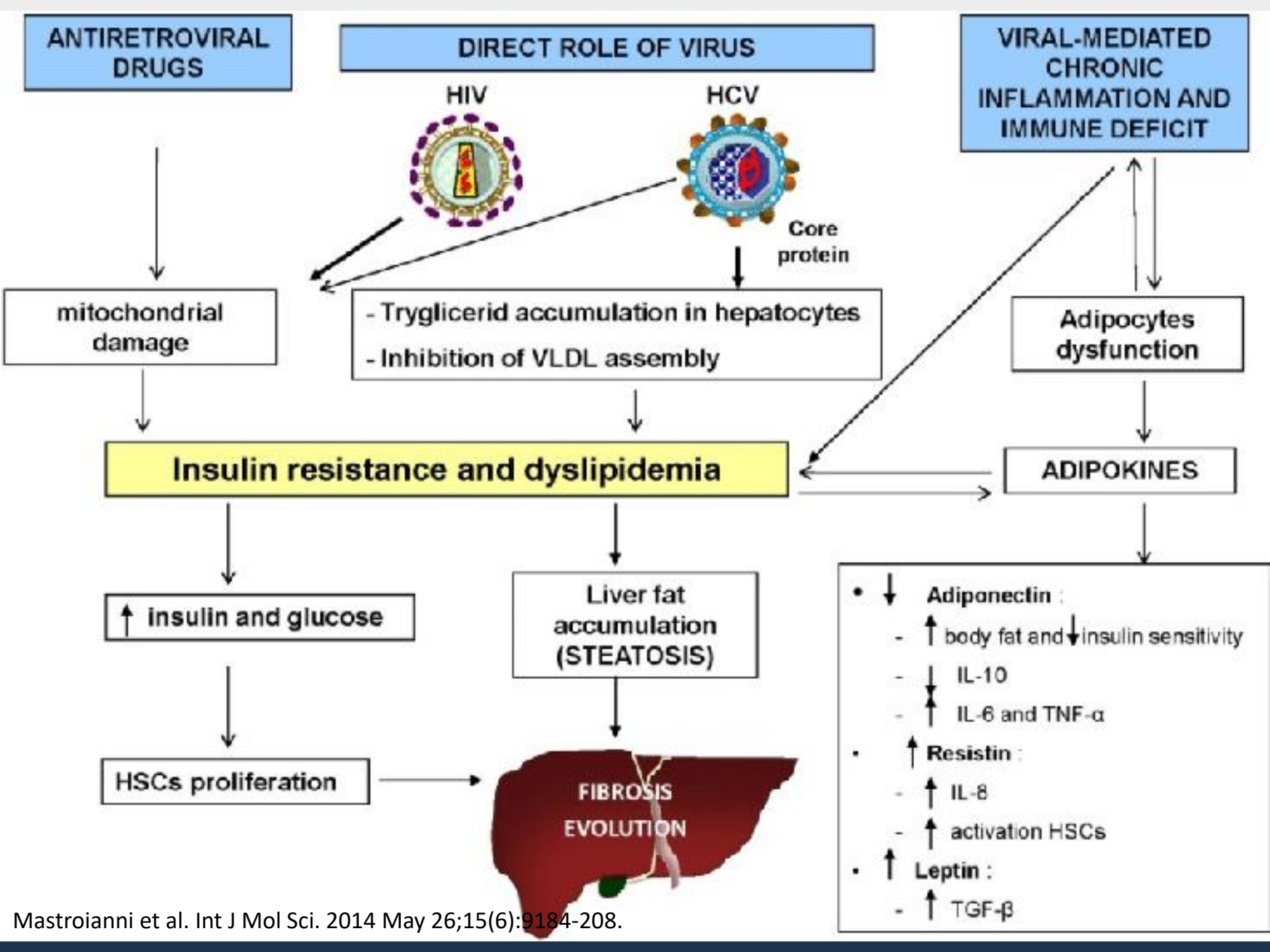
- 27 studies (*n* = 1,349)
- Topiramate and Metformin are effective add-on treatments
- Weight loss(kg)= -2.54 (95% CI: -3.29, -1.79) and -2.95 (95% CI: -5.87, -0.03)
- 3 studies exenatide once-weekly and liraglutide provided participant-level data (n = 164)
- Weight loss 3.71 kg ($p < 0.001$) & NNT ≥5% body weight loss = 3.8
- Glp-1 RA-reduced body weight particularly clozapine/olanzapine-treated patients (very limited data)

Front Pharmacol. 2018 Nov 28;9:1393
Diabetes Obes Met 2019 Feb;21(2):293-302.

Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors



Siskind D et al. Diabetes Obes Metab. 2019 Feb;21(2):293-302



Mastroianni et al. Int J Mol Sci. 2014 May 26;15(6):9184-208.

Protease Inhibitors

Insulin resistance and high cholesterol

- atazanavir (Reyataz)
- darunavir (Prezista)
- fosamprenavir (Lexiva)
- indinavir (Crixivan)
- lopinavir/ritonavir (Kaletra)
- nelfinavir (Viracept)
- ritonavir (Norvir)
- saquinavir (Invirase)
- atazanavir/cobicistat (Evotaz)
- darunavir/cobicistat (Prezcobix

Nucleotide Reverse Transcriptase Inhibitors

Lipodystrophy and NASH

- zidovudine (Retrovir)
- lamivudine (Epivir)
- abacavir sulfate (Ziagen)
- didanosine (Videx)
- delayed-release didanosine (Videx EC)
- stavudine (Zerit)
- emtricitabine (Emtriva)
- tenofovir disoproxil fumarate (Viread)
- lamivudine and zidovudine (Combivir)
- abacavir and lamivudine (Epzicom)
- abacavir, zidovudine, and lamivudine (Trizivir)
- tenofovir disoproxil fumarate and emtricitabine (Truvada)
- tenofovir alafenamide and emtricitabine (alafenamide)

Lipodystrophy

- Potential interventions include:

1. modification of the antiretroviral regimen
2. surgical correction
3. ? Use of diabetes medications

- 14 clinical trials to examine whether thiazolidinediones could be useful in the treatment of HAART-associated metabolic complications
- Results of these studies indicate very modest, if any, effect on lipoatrophy
- Probably due to ongoing HAART negating the benefit

Potential interventions for lipodystrophy

Lipoatrophy	Fat accumulation
Switch thymidine analogue (stavudine or zidovudine) to abacavir or tenofovir	Diet and exercise
Injectable fillers for facial lipoatrophy	Metformin (in patients with diabetes mellitus)
Pioglitazone (in patients with insulin resistance)	Tesamorelin
	Surgery (eg, liposuction of dorsocervical fat pad or reduction mammoplasty)

UpToDate®

Sutinen J.*PPAR Res*. 2009;2009:373524
https://www.uptodate.com/contents/treatment-of-hiv-associated-lipodystrophy

HIV and Metformin and lipodystrophy/fat accumulation

- May improve insulin sensitivity, it may not be well tolerated by cachexic patients.
- Metformin is more likely to cause diarrhea than other drugs
- Avoided in combination with drugs such as stavudine given risk for Lactic Acidosis
- Abacavir, lamivudine and tenofovir are the least likely drugs to cause elevation of lactate levels
- Metformin was associated with a significant decrease in appendicular fat mass compared with placebo (-686.0 vs 161.0 g; P=0.03). There was no sig change in lipid profile or insulin sensitivity between the two groups at 24 weeks

Kohli R et al. HIV Med. 2007 Oct;8(7):420-6 Kalra S et al Diabetol Metab Syndr. 2011 Jan 14;3(1):2

Protective Effect of GLP-1 Receptor Agonists (GLP-1 RA) and SGLT2 Inhibitors (SGLT2i) against Adverse Cardiovascular (CV) Events in HIV and Type 2 Diabetes Mellitus (T2DM)

Table 1: Association between GLP-1 RA/SGLT2i agonists vs. Metformin and adverse cardiovascular events						
	Cases (GLP1/SGLT2 + Metformin)		Controls (Metformin only)			
	N (events)	Risk %	N (events)	Risk %	OR	95% CI
Acute heart failure (GLP-1 RA/SGLT2i + metformin)	60	6.06%	660	9.52%	0.6129	0.463, 0.8005
Myocardial infarction (GLP-1 RA/SGLT2i +metformin)	100	11%	970	15.57%	0.6695	0.5358, 0.8304
Acute heart failure (GLP-1 RA +metformin)	20	6%	660	9.52%	0.6334	0.39, 0.9844
Myocardial infarction (GLP-1 RA +metformin)	30	9.68%	970	15.57%	0.581	0.3901, 0.8418
Acute heart failure (SGLT2i + metformin)	30	6.82%	660	9.52%	0.6952	0.4682, 1.003
Myocardial infarction (SGLT2i +metformin)	40	10.00%	970	15.57%	0.6026	0.4267, 0.8338

OMAR A. ALABER et al. Diabetes 2020;69:1433-P

- 2 case reports of use in HIV and Type 2 diabetes and GLP-1-RA

Diabetes Care. 2012;35(5):e34

Diabetes Metab. 2015 Feb;41(1):102-3.

Summary

- Many psychiatric illness are independently associated with obesity, diabetes and other metabolic issues
- Many psych medications induce weight gain and some induce weight loss
- Protease inhibitors and nucleotide reverse transcriptase inhibitors cause worsening metabolic issues
- Metformin and GLP-RA may abate some of related weight gain but research limited especially in GLP-RA
- Lifestyle modifications always important but challenging in pts with mental health issues and/ or other co-morbidities