Safety and Compliance of Psychopharmacological Therapy

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Does it matter?

- Increased risk of poor medication adherence[1].
- Increased risk of HIV disease progression[2].
- Maybe poor virological response to treatment[3].
- Improves quality of life[4].

1 Kalichman SC. Psychosom Med (2008), 2 Leserman J. Psychosom Med (2008), Pence BW et al. J Acquir Immune Defic Syndrom (2007), [4] Elliot AJ et al. Gen Hosp Psychiatry (2007)

Psychopharmacology and HIV

- Psychiatric comorbility in people HIV positive is highly prevalent and poly-pharmacy is common.

- Special issue about metabolic syndrome associated to both SGA and HAART.

Psychiatric comorbility in HIV

- Is overwhelmingly prevalent.
- 1:2 suffer with a DSM-IV Axis I disorder.
  - Stable over the last decade[1,2].
  - Men are more affected than women.
    - 63.91% *vs.* 37.45%
  - Similar in different geographical areas
    - USA[2].
    - India[3].
    - Kenya[4].

[1] Bing EG at al. Archives General Psychiatry 2001, [2] Lopes et al. J Clin Psychiatry 2012, [3] Nebhinani N et al. J Psychosom Res 2011, [4] Kamau JW et al, AIDS Care 2012.

Psychiatric comorbility in HIV

	Men (%)	Women (%)
Mood Disorder	29.86	10.78
Anxiety Disorder	33.43	23.74
Substance Misuse	38.53	19.66

Lopes et al. Gender, HIV Status and Psychiatric Disorders: Results from the National Epidemiologic Survey on alcohol and Related conditions. J Clin Psychiatry 2012 (March) 73:3.

antidepressants in HIV

- Some good news: they work!
- Combination with CBT and/or psychological interventions.
- Improve adherence to antiretroviral treatment.
- Improve the quality of life.

Dalessandro M, J Clin Psychopharmacol (2007), Elliot AJ. Gen Hosp Psychiatry (2002)

antidepressants

- Tricyclic Antidepressants (TCA)
  - Efficacious (74% response rates)
  - No changes in $CD4^{+}$.
  - High discontinuation rates due to adverse side effects[1,2] .
- SSRIs
  - As efficacious as TCA
  - With less side effects and lower discontinuation ratios [2.]

[1] Rabkin Am J Psychiatry (1994), [2]Elliot et al AM j Psychiatry (1998)

SSRI: efficacy and safety

- Efficacy: High with all of the SSRI studies
  - Paroxetine: response rates >75%
  - Fluoxetine: response rates >70%
  - Sertraline: response > 70%
  - Citalopram: response >70%

- Safety
  - No changes in changes in CD4: fluoxetine and sertraline,
  - CYP450 interactions!
    - HARRT and Antidepressants use same pathway!
    - Serotoninergic syndrome in fluoxetine and ritonavir/efavirenz/saquinavir
    - Fluvoxamine increases nevirapine levels.
    - Nevirapine decreases fluoxetine but not fluvoxamine.
    - Ritonavir doesn't change escitalopram levels.

SSRI: efficacy and safety

- Recommendations
  - Reduction initial dose
  - Slow titration.
  - Close monitoring for toxic reaction.

- Look for interactions!
  - http://www.interaccionesvih.com/login.php
  - http://www.hiv-druginteractions.org/

SSRI: efficacy and safety

Drug Interaction Charts

Step 1	Searching by: **Abacavir, Efavirenz**	**Amend Selection**
Step 2	Searching by: **Antidepressants, Antiretrovirals (NNRTIs), Antiretrovirals (Nucleoside/tide Analogues)**	**Amend Selection**
Step 3	Choose one or more combination drugs and deselect any HIV drugs that are not required as rows	**Next >>**
Step 4	View results	

HIV Drug look-up chart

Antidepressants	Antiretrovirals (NNRTIs)	Antiretrovirals (Nucleoside/tide Analogues)
☐ Amitriptyline	☐ Delavirdine	☑ Abacavir
☐ Bupropion	☑ Efavirenz	☐ Didanosine (ddI)
☑ Citalopram	☐ Etravirine	☐ Emtricitabine (FTC)
☑ Clomipramine	☐ Nevirapine	☐ Lamivudine (3TC)
☑ Desipramine	☐ Rilpivirine	☐ Stavudine (d4T)
☑ Doxepin		☐ Tenofovir
☑ Fluoxetine		☐ Zidovudine (AZT/ZDV)
☑ Lithium		
☑ Mirtazapine		
☑ Nefazodone		
☐ Nortriptyline		
☐ Paroxetine		
☐ Sertraline		
☐ Trazodone		
☐ Venlafaxine		

Previous Finish

SNRI and other antidepressants

- Venlafaxine
  - Interaction with CYP450: lowers levels of indinavir
- Duloxetine
  - Increase liver enzymes: caution in people with coinfection with CHV.
- Bupropion
  - Efficacious, well tolerated
  - Several interactions with CYP450 and antiretrovirals.
- Mirtazapine
  - efficacious

Antipsychotics and HIV

AP: two main scenarios

- Acute and transient use of antipsychotic: interactions!
- Chronic use of antipsychotic in HIV+ patients.

Acute use of antipsychotic

- Watch out for interactions!
  - Delirium, manic states, etc…
  - CYP450
  - Same preventions than before:
    - Star low and go slow.
    - Close monitoring
  - Parkinsonian symptoms are seen in HIV+ in absence neuroleptic exposure.

[1] Bing EG at al. Archives General Psychiatry 2001, [2] Lopes et al. J Clin Psychiatry 2012, [3] Nebhinani N et al. J Psychosom Res 2011, [4] Kamau JW et al, AIDS Care 2012.

Chronic use of antipsychotic

- People with schizophrenia have a greater risk of HIV.
- Estimated prevalence 1.5%

Use of Medicaid Data to Explore Community Characteristics Associated with HIV Prevalence Among Beneficiaries with Schizophrenia

PUBLIC HEALTH REPORTS / 2011 SUPPLEMENT 3 / VOLUME 126

Both atypical antipsychotics and HAART increase the risk of developing metabolic syndrome

What is the metabolic syndrome?

Cluster of cardiovascular risk factors that increase:

- risk of heart attack
- risk of overall mortality
- risk of stroke

Different definitions of metabolic syndrome (MetS).

Criteria	NCEP ATP III[a] (3 out of 5)	IDF[b] (Obesity plus 2 others)
Central obesity (waist circumference)	≥102 cm (men), ≥88 cm (women)	>94 cm (men), >80 cm (women)
Triglycerides	TG≥150 mg/dl	TG≥150 mg/dL (or on lipid treatment)
HDL-cholesterol	HDL-C <40 mg/dL (men), <50 mg/dL (women)	HDL-C (or on lipid treatment) <40 mg/dL (men), <50 mg/dL (women)
Blood pressure	≥130/85 mm Hg	≥130/85 mm Hg (or being on antihypertensive treatment)
Fasting plasma glucose	≥100 mg/dl	≥100 mg/dL

[a] Expert Panel NCEP ATP III (2001).
[b] IDF (2006).

High prevalence of MS in schizophrenia

Age-specific metabolic syndrome prevalence in fasting CATIE subjects and randomly selected age-, gender-, and race/ethnicity-matched NHANES III sample by gender

	CATIE (%±SE)	NHANES (%±SE)
Males		
20–29	27.0±4.2	7.8±2.5
30–39	43.9±4.7	12.3±3.1
40–49	39.8±3.8	24.0±3.1
50–59	30.5±4.7	36.2±5.0
60–69	55.6±17.6	33.3±16.7
Females		
20–29	47.1±12.5	0±0
30–39	45.7±8.5	8.8±4.9
40–49	58.8±6.0	24.3±5.2
50–59	41.3±7.3	43.5±7.4
60–69	88.9±11.1	55.6±17.6

Mortality in schizophrenia

Twenty-five year mortality of a community cohort with schizophrenia

Steve Brown, Miranda Kim, Clemence Mitchell and Hazel Inskip

BJPsych | The British Journal of Psychiatry (2010) 196, 116–121. doi: 10.1192/bjp.bp.109.067512

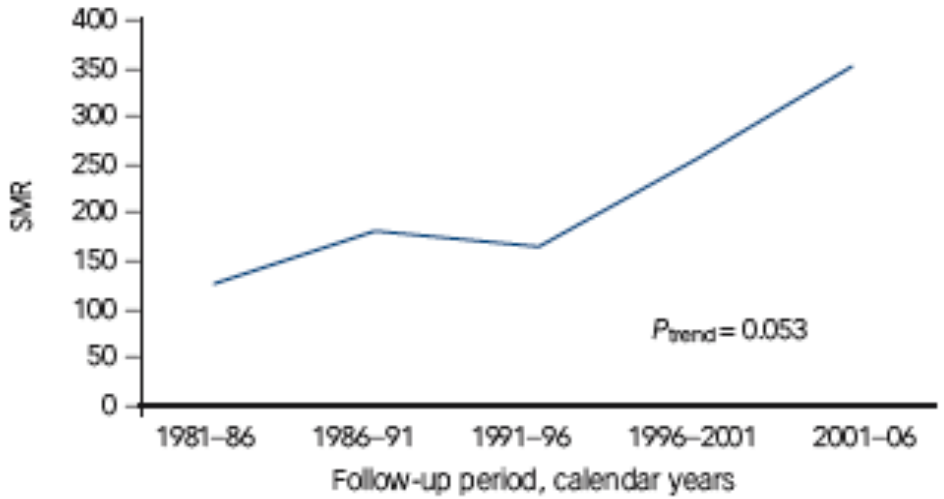


Fig. 4 Changes in cardiovascular disease standardised mortality ratios (SMRs) in 5-year periods of a community cohort of 370 people followed over 25 years.

Reduction of lifespan in SMI/ CMI

- 15-20% lifespan reduction in people suffering with schizophrenia[1].
- 10-15% lifespan reduction in people suffering with MDD[2].

Table 2. Life expectancy at birth of people with specific mental disorders in the period of 2007–09 (N = 31,719).

Diagnosis	Male		Female	
	Life Expectancy (95% CI, number of deaths)	Difference from male UK population*	Life Expectancy (95% CI, number of deaths)	Difference from female UK population*
Any Serious Mental Illness^	64.5 (63.3–65.6, n = 243)	−12.9	69.9 (68.7–71.0, n = 203)	−11.8
Schizophrenia (F20)^	62.8 (61.6–64.10, n = 196)	−14.6	71.9 (71.0–72.8, n = 126)	−9.8
Schizoaffective disorder (F25)^	69.4 (68.3–70.5, n = 16)	−8.0	64.1 (60.9–67.2, n = 28)	−17.5
Bipolar affective disorder (F31)^	67.3 (66.1–68.5, n = 43)	−10.1	70.4 (69.5–71.4, n = 65)	−11.2
Substance use disorders (F10–F19)^	63.9 (62.7–65.0, n = 254)	−13.6	66.9 (65.5–68.3, n = 94)	−14.8
Depressive episode and recurrent depressive disorder (F32–F33)^	66.8 (65.6–67.9, n = 284)	−10.6	74.4 (73.5–75.3, n = 336)	−7.2

*Life expectancy at birth 2006–08 in UK: Male = 77.4 years; Female = 81.6 years [27].
^Significant difference between genders.
doi:10.1371/journal.pone.0019590.t002

PLoS one May 2011 | Volume 6 | Issue 5 |

[1] Saha et al. Arch General Psychiatry 2007, [2] Chang et al. BMC Psychiatry 2010

So, what is the impact of SGA in Met Syndrome?

Are all SGA equal?

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

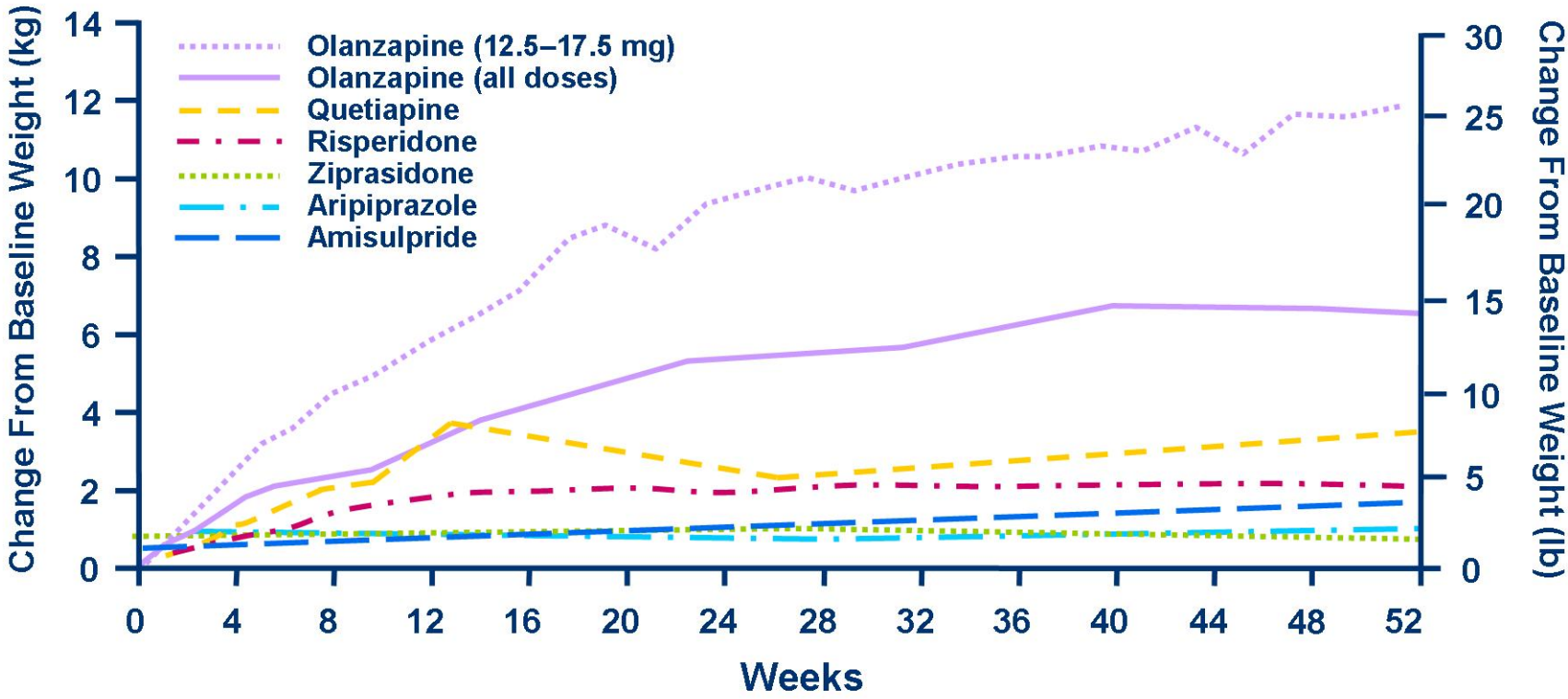
Drug	Weight gain	Risk for diabetes	Worsening lipid profile
clozapine	+++	+	+
olanzapine	+++	+	+
risperidone	++	D	D
quetiapine	++	D	D
aripiprazole*	+/-	-	-
ziprasidone*	+/-	-	-

+ = increase effect; - = no effect; D = discrepant results

* newer drugs with limited long-term data

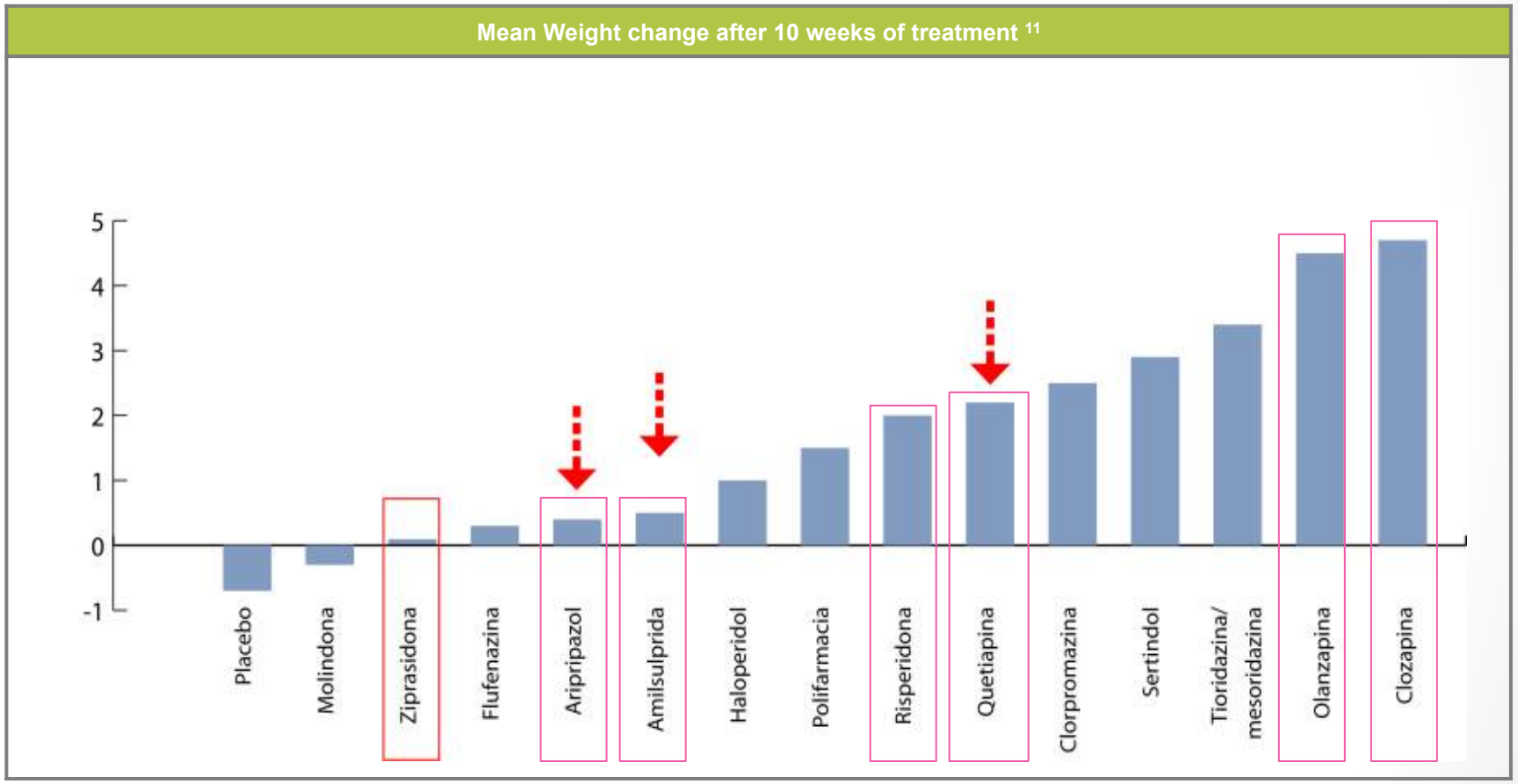
One-Year Weight Gain While on Treatment With an Antipsychotic

Mean Change From Baseline Weight

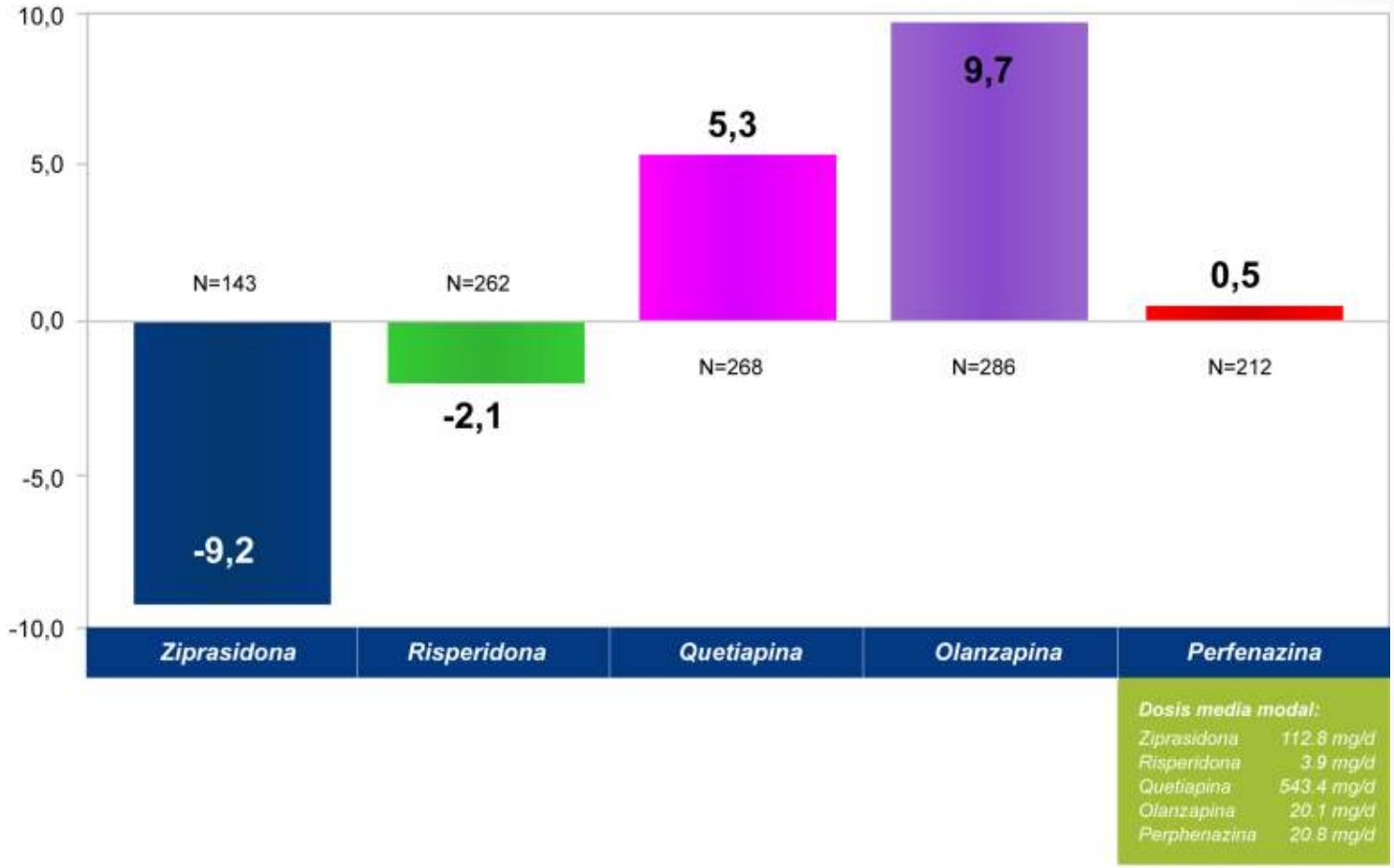


Adapted from Casey DE. *Am J Med.* 2005;118(suppl 2):15S-22S.
Leucht S et al. *Psychopharmacology.* 2004;173:112-115.

Weight gain and antipsychotics

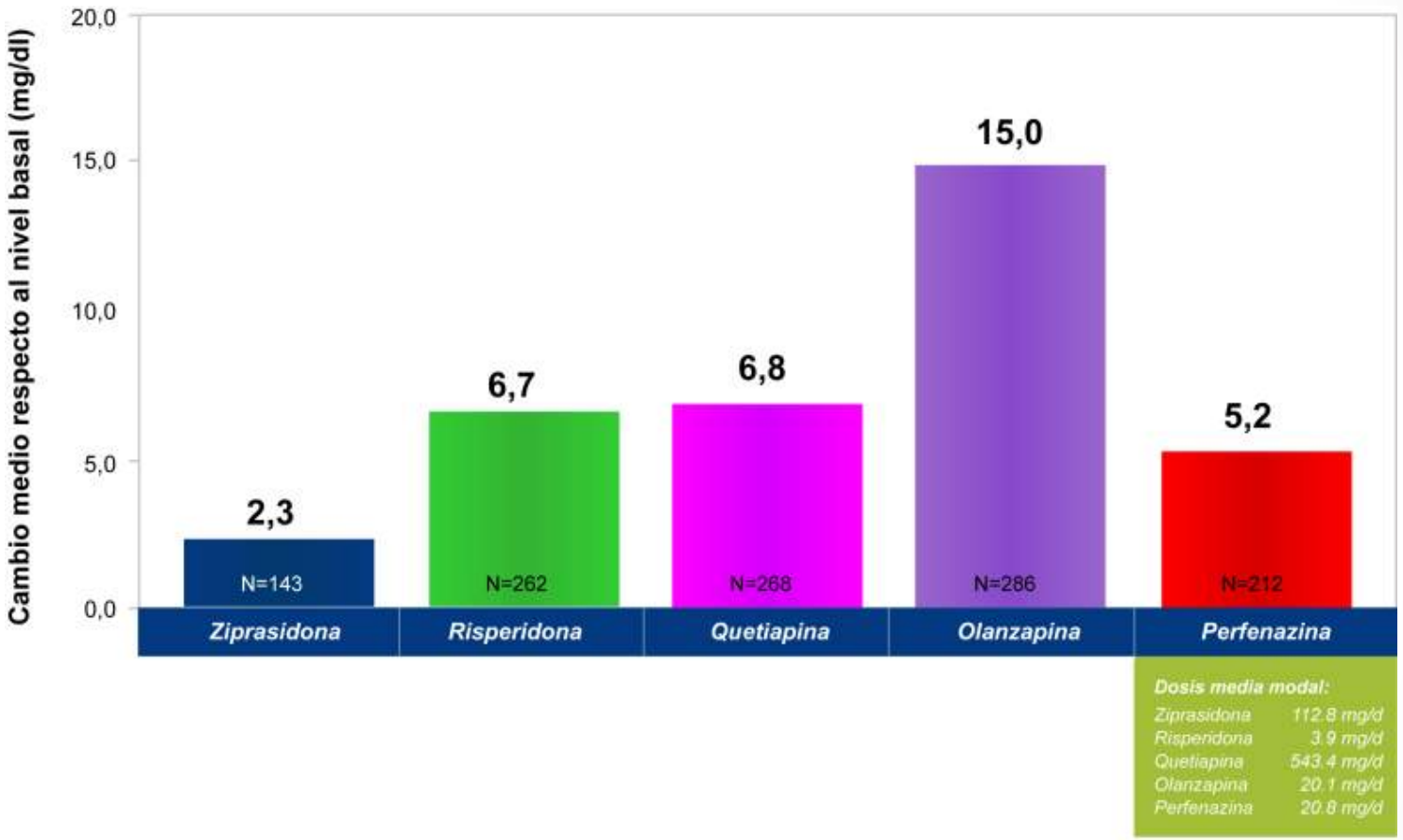


CATIE study: Total Cholesterol



Lieberman JA, et al. N Engl J Med. 2005;353:1209-1223

CATIE: Glucose level



Lieberman JA, et al. N Engl J Med. 2005;353:1209-1223

Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial

Lancet 2008; 371: 1085–97

René S Kahn, W Wolfgang Fleischhacker*, Han Boter, Michael Davidson, Yvonne Vergouwe, Ireneus P M Keet, Mihai D Gheorghe, Janusz K Rybakowski, Silvana Galderisi, Jan Libiger, Martina Hummer, Sonia Dollfus, Juan J López-Ibor, Luchezar G Hranov, Wolfgang Gaebel, Joseph Peuskens, Nils Lindefors, Anita Riecher-Rössler, Diederick E Grobbee, for the EUFEST study group†*

Table 4

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	p value
Mean dose before discontinuation of treatment (mg/day [SD])	3·0 (1·2)	450·8 (171·9)	12·6 (4·7)	498·6 (201·4)	107·2 (35·0)	
Maximum (or higher) dose received*	56/92 (61%)	26/100 (26%)	54/103 (52%)	39/104 (38%)	37/79 (47%)	<0·0001
Discontinuation for any cause†	63/103 (72%)	32/104 (40%)	30/105 (33%)	51/104 (53%)	31/82 (45%)	
Weight‡						
Overweight (BMI ≥25 kg/m²)	16/43 (37%)	31/72 (43%)	45/83 (54%)	25/55 (45%)	14/43 (33%)	0·585
Weight gain >7% from baseline	23/43 (53%)	45/72 (63%)	71/83 (86%)	36/55 (65%)	16/43 (37%)	0·053
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)	<0·0001
Fasting glucose (mmol/L)§						
Hyperglycaemia‖	6/33 (18%)	11/53 (21%)	19/63 (30%)	9/41 (22%)	7/32 (22%)	0·794
Change from baseline						
Mean (SE)	0·4 (0·2)	0·5 (0·1)	0·5 (0·1)	0·5 (0·1)	0·2 (0·2)	
Median (IQR)	0·3 (0·0 to 0·9)	0·5 (0·0 to 1·0)	0·5 (0·1 to 1·0)	0·4 (0·0 to 0·9)	0·3 (−0·2 to 0·9)	
Per month in study	0·04 (0·03)	0·07 (0·02)	0·07 (0·02)	0·06 (0·02)	0·04 (0·02)	0·699

(Continues on next page)

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone	p value
(Continued from previous page)						
Cholesterol (mmol/L)§						
Hypercholesterolemia**	15/33 (45%)	24/53 (45%)	37/66 (56%)	12/43 (28%)	17/32 (53%)	0·276
Change from baseline						
Mean (SE)	0·5 (0·3)	0·7 (0·2)	0·8 (0·1)	0·6 (0·1)	0·4 (0·2)	
Median (IQR)	0·7 (−0·2 to 1·3)	0·5 (0·1 to 1·4)	0·7 (0·2 to 1·3)	0·6 (0·1 to 1·1)	0·3 (−0·2 to 1·0)	
Per month in study	0·04 (0·05)	0·11 (0·02)	0·11 (0·02)	0·07 (0·02)	0·04 (0·02)	0·144
HDL (mmol/L)§						
Low concentration of HDL††	6/32 (19%)	15/53 (28%)	16/65 (25%)	8/43 (19%)	5/32 (16%)	0·894
Change from baseline						
Mean (SE)	−0·1 (0·1)	−0·2 (0·0)	−0·1 (0·0)	−0·1 (0·1)	−0·1 (0·0)	
Median (IQR)	−0·1 (−0·2 to 0·1)	−0·1 (−0·3 to 0·1)	−0·1 (−0·4 to 0·0)	0·0 (−0·2 to 0·1)	−0·1 (−0·2 to 0·1)	
Per month in study	−0·02 (0·01)	−0·02 (0·01)	−0·02 (0·01)	−0·01 (0·01)	−0·01 (0·01)	0·894
LDL (mmol/L)§						
High concentration of LDL‡‡	16/31 (52%)	23/52 (44%)	35/66 (53%)	13/42 (31%)	13/32 (41%)	0·602
Change from baseline						
Mean (SE)	0·5 (0·2)	0·7 (0·2)	0·7 (0·1)	0·7 (0·1)	0·3 (0·1)	
Median (IQR)	0·4 (0·0 to 1·5)	0·5 (−0·1 to 1·2)	0·6 (0·1 to 1·3)	0·7 (0·1 to 1·0)	0·1 (−0·2 to 0·9)	
Per month in study	0·05 (0·04)	0·11 (0·03)	0·09 (0·02)	0·09 (0·02)	0·03 (0·02)	0·303
Fasting insulin (mU/L)§						
Change from baseline						
Mean (SE)	2·0 (1·4)	8·6 (3·1)	2·5 (3·9)	2·1 (1·2)	0·1 (2·0)	
Median (IQR)	3·0 (−2·3 to 6·0)	2·5 (−0·3 to 11·5)	4·0 (0·3 to 11·0)	1·0 (−1·0 to 3·5)	0·0 (−3·0 to 4·0)	
Per month in study	0·31 (0·24)	1·04 (0·36)	0·58 (0·35)	0·11 (0·14)	−0·13 (0·25)	0·080
Triglycerides (mmol/L)§						
Hypertriglyceridaemia§§	13/33 (39%)	19/53 (36%)	26/66 (39%)	11/42 (26%)	10/32 (31%)	0·908
Change from baseline						
Mean (SE)	0·2 (0·1)	0·5 (0·1)	0·3 (0·1)	0·3 (0·1)	0·1 (0·2)	
Median (IQR)	0·1 (−0·2 to 0·8)	0·4 (0·1 to 0·9)	0·3 (−0·1 to 0·7)	0·2 (−0·2 to 0·7)	0·1 (−0·3 to 0·4)	
Per month in study	0·02 (0·02)	0·07 (0·02)	0·04 (0·02)	0·04 (0·02)	0·02 (0·02)	0·439

METABOLIC SYNDROME AND RELATED DISORDERS
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Metabolic Abnormalities and Coronary Heart Disease Risk in Human Immunodeficiency Virus–Infected Adults

Clive R. Pullinger, Ph.D.,[1,2] Bradley E. Aouizerat, Ph.D.,[2,3] Caryl Gay, Ph.D.,[4] Traci Coggins,[4]

HAART and Met Syndrome?

Original article

The assessment of metabolic syndrome in UK patients with HIV using two different definitions: CREATE 2 study

Current Medical Research & Opinion Vol. 27, No. 1, 2011, 63–69

Monitoring

Monitoring recommendations for patients with HIV on HAART[a] or with SMI on SGAs.[b]

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	5 years
Personal/family history	✓SGA ✓HIV					✓SGA ✓HIV	
Weight (BMI)	✓SGA ✓HIV	✓SGA ✓HIV[c]	✓SGA	✓SGA ✓HIV[c]	✓SGA ✓HIV[c]		
Waist circumference	✓SGA ✓HIV					✓SGA ✓HIV	
Blood pressure	✓SGA ✓HIV	✓HIV[c]		✓HIV[c]	✓HIV[c]	✓SGA ✓HIV	
Fasting blood glucose	✓SGA ✓HIV			✓HIV[d]		✓SGA ✓HIV	
Fasting lipid profile	✓SGA ✓HIV			✓SGA ✓HIV[d]		✓HIV	✓SGA

[a] Schambelan et al. (2002).
[b] ADA/APA/ACE (2004).
[c] HIV Patients have weight and BP checked with each visit.
[d] Lipid and glucose re-checked after each change in therapy.

Metabolic management

- Individualized care
- Interventions
  - Lifestyle modification
    - To reduce legal and illegal drug use
    - Exercise!
  - Adjunt therapy
    - For glucose dysregulation
    - For dyslipidemia
    - For high blood pressure
  - Switch therapy?
    - For HIV
    - Antipsychotics.

Compliance of medication

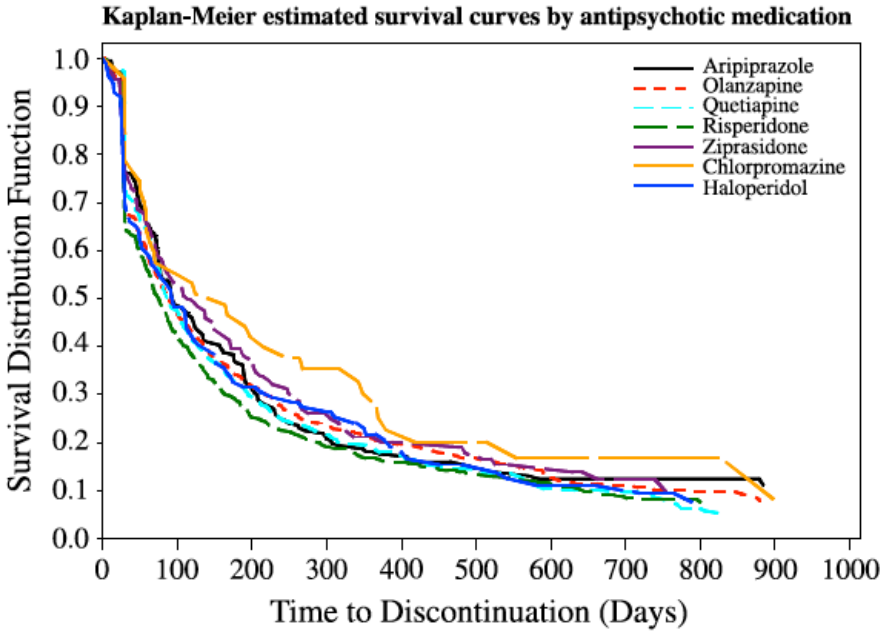
Time to discontinuation of first- and second-generation antipsychotic medications in the treatment of schizophrenia

Julie Kreyenbuhl [a,b,*], Eric P. Slade [a,b], Deborah R. Medoff [a,b], Clayton H. Brown [a,c], Benjamin Ehrenreich [b], Joseph Afful [b], Lisa B. Dixon [a,b]

Schizophrenia Research 131 (2011) 127–132

Table 2
Unadjusted median time to discontinuation by antipsychotic medication.

Index drug	Number of index episodes	Median time to discontinuation (days)	95% CI
Aripiprazole	214	93	(76–131)
Olanzapine	539	90	(75–105)
Quetiapine	394	87	(77–105)
Risperidone	690	76	(65–87)
Ziprasidone	139	114	(79–170)
Chlorpromazine	47	164	(59–268)
Haloperidol	114	95	(58–127)



Beyond the Usual Suspects: Positive Attitudes Towards Positive Symptoms Is Associated With Medication Noncompliance in Psychosis

Schizophrenia Bulletin
doi:10.1093/schbul/sbs005

Table 2. Reasons for Discontinuation of Antipsychotic Medication (Sorted in Descending Frequency for the Present Study, Multiple Endorsements Were Allowed)

Variable	Present Study
1. Too many side-effects	80%
2. Did not need antipsychotics in my view	58%
3. Medication intake amounts to stigma as being ill	31%
4. I distrust my physician/therapist	31%
5. I had the feeling that taking medication was the same as acknowledging that all I have experienced was untrue (although this is not the case)	28%
6. I reject medication in general	28%
7. Forgot intake	21%
8. Friends/relatives advised me not to take it	20%
9. During psychosis, I had a feeling of importance and power which I did not want to miss	18%
10. During my illness, I become another person and for this reason I need this state from time to time	18%
11. Do not work for me	16%
12. I falsely assumed that I should only take them when having acute symptoms	15%
13. Medication is too expensive for long-term treatment	8%
14. I missed the voices	7%
15. I had fears that acquaintances might detect medication boxes	3%
16. Intake was too complicated	2%

Take home messages

- Psychiatric comorbility is highly prevalent
- Depression and anxiety are more dfreqeuntly associated
- Antidepressants are efficacious
- Potential interactions between antiretrovirals, antidepressants and antipsychotics
- Metabolic syndrome: both SGA and HAART are risk factor
- Compliance with medication is key for long term prognosis
  - Use of Depot medication?

Thank you!

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