THE USE OF ANTIPSYCHOTICS IN HIV-INFECTED PATIENTS

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AGENDA

- indications
- drug selection
- side effects (risk of metabolic syndrome)

- ◇ where we are
- ◇ what we know
- ◇ which are the knowledge gaps
- ◇ which are the priorities
- ◇ what is next

WHY?

INTRODUCTION

- SMI can increase the risk of acquiring HIV
- SMI can be the result of having a chronic/rapid fatal disease (stigma)
- SMI can be engendered by, or overlap with, central nervous system complications of the infections and its treatments.

[Ferrando & Loftus 2008]

INTRODUCTION

- Psychiatric diseases are common in HIV patients [Bing 2001, Gaynes 2008]
- Persons with severe mental illness (SMI) are disproportionately affected by HIV/AIDS. [Meade & Sikkema, 2007]
- The prevalence of HIV infection among persons with severe mental illness (SMI) has been estimated to range between 3.1 and 22.9% [Cournos &McKinnon, 1997; Citron et al. 2005; Lee, 2011]
- SMI could negatively affect retention to HIV care [Joska, 2014]

RISK FACTORS INFLUENCING HIV TRANSMISSION IN SMI POPULATION

- **Psychopatology**: low self esteem, suicidal ideation, substance-induced behavioral disinhibition, hypersexuality, , trading sex for drugs, sexual compulsivity and sensation seeking) [McKinnon et al. 2001 ; Meade 2006]
- Lack of **communication skills** and cognitive skills (McKinnon et al., 2002, Meade & Sikkema 2005)
- Poor assesment of sexual risk; lack of knowledge on how to protect sex (Kloos et al., 2005),
- Difficult to engage or mantain a long-term relationship (do to multiple hospitalization, poor social life, relationship with patients) (Wright & Gayman ,2005; McKinnon 2002).
- History of trauma (physical/sexual abuse) (Devieux et al. 2007, Meade & Sikkema 2007, Meade et al. 2009,)

INDICATIONS

Psychotic symptoms
[thought disorders, hallucinations, delusions]

- **schizophrenia** and other psychosis
- **mood disorders** with psychotic symptoms (mania, depression) [Cipriani, 2011]
- **augmenting agents** for treatment-resistant depression
- "off-label" for various other disorders, such as treatment-resistant anxiety disorders, **personality disorders**.

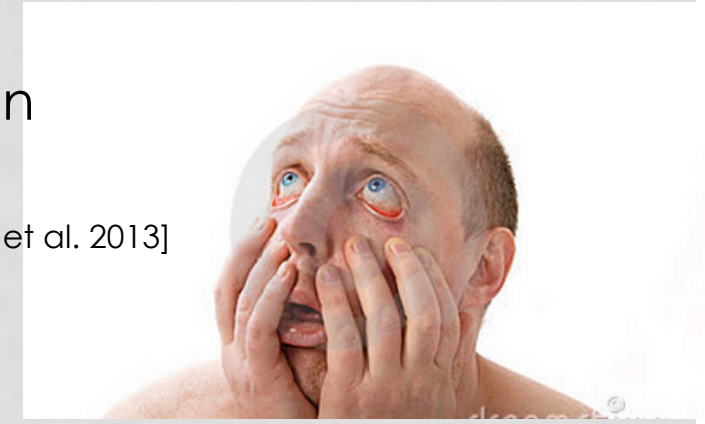
PSYCHOTIC SYMPTOMS

DIFFERENTIAL IN HIV+ POPULATION

- **delirium** (criptococcal meningitis [Jacob 2013], visual hallucinations induced by CMV reninitis, neurosiphilis)
- AIDS **dementia** (delusional parasitosis)[Musso MW, 2013]
- **substance** intoxication or withdrawal
- **induced by ARVs** (e.g. efavirenz [Hinsch MC 2014])or other drugs (e.g. trimethoprim/ sulfamethoxazole + steroids for Pneumocystis Jirovecii pneumonia) [Lee KY, 2012]

MAIN PROBLEMS

1. **Few RCTs**
2. **CNS micro or macro lesions** → unusual clinical manifestations and/or unexpected drugs side effects (e.g. FGA)
3. **Polypharmacy** (defined as >5 meds) [**c**ART, aging population]
   - it is associated with poorer adherence → adding medication may diminish the effectiveness of ART (mortality and hospitalization)
   - drug-drug interactions (ARVs are all metabolized by CYP450)
4. **Enhanced susceptibility to side effects** due to :
   - decreased organ system reserve
   - liver disease/fibrosis, HCV-coinfection
   - chronic inflammation
   - ongoing immune dysfunction [Edelman et al. 2013]
5. **Risk of drug misuse/abuse**



WHAT HAS BEEN STUDIED SO FAR?

- **1 RCT** (Breibart 1996): 30 hiv+ with delirium. HALO=clorpromazine.
- **Cases reports, open label studies**

YES

- HALOPERIDOL
- ARIPIPRAZOLE
- CLORPROMAZINE
- CLOZAPINE
- OLANZAPINE
- QUETIAPINE
- RISPERIDONE
- ZIPRASIDONE

NO

- AMISULPRIDE
- ASENAPINE
- BLONANSERINE
- ILPERDIONE
- LURASIDONE
- PALIPERIDONE
- SERTINDOLE
- ZOTEPINE

MAIN FINDINGS

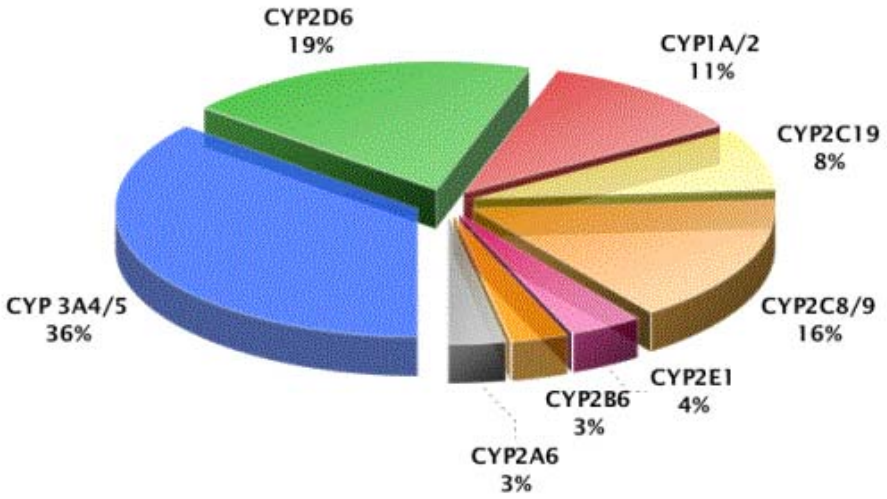
- **HALOPERIDOL**
  - positive symptoms of psychosis in 13 male hiv+ (Sewell et al, 1994)
  - high rates of EPS and TD in young AIDS pts (Caligiuri et al, 1999)
- **ARIPIPRAZOLE**
  - acute psychosis and catatonia (Huffman&Fricchione, 2005)
  - + citalopram for resistant depression, somatoform disorder and panic disorder (Cecchelli, et al 2010)
- **CLOZAPINE**
  - psychotic symptoms and drug induced Parkinson in 6 hiv pts (Lera & Zirulnik, 1999)
  - refractory schizophrenia 2 HIV+ women

MAIN FINDINGS

- **OLANZAPINE**
  - psychotic depression (Meyer, 1998) previously treated with typical AP (EPS, TD)
  - criptococcical meningitis-induced mania (Spiegel et al 2011)
- **QUETIAPINE**
  - first line choice by clinicians for psychosis and secondary mania (Freudenreich et al., 2010)
- **RISPERIDONE**
  - agitation in HIV/AIDS dementia (Lodge, 1998; Belzie, 1996)
  - delusional disorders (Maha & Goetz, 1998)
  - acute psychosis (Zilikis et al 1998)
  - catatonia and mania (Prakash & Bagepally, 2012)
- **ZIPRASIDONE**
  - mania (Spiegel et al, 2010)

DRUG-DRUG INTERACTIONS

Proportion of Drugs Metabolized by P450 Enzymes

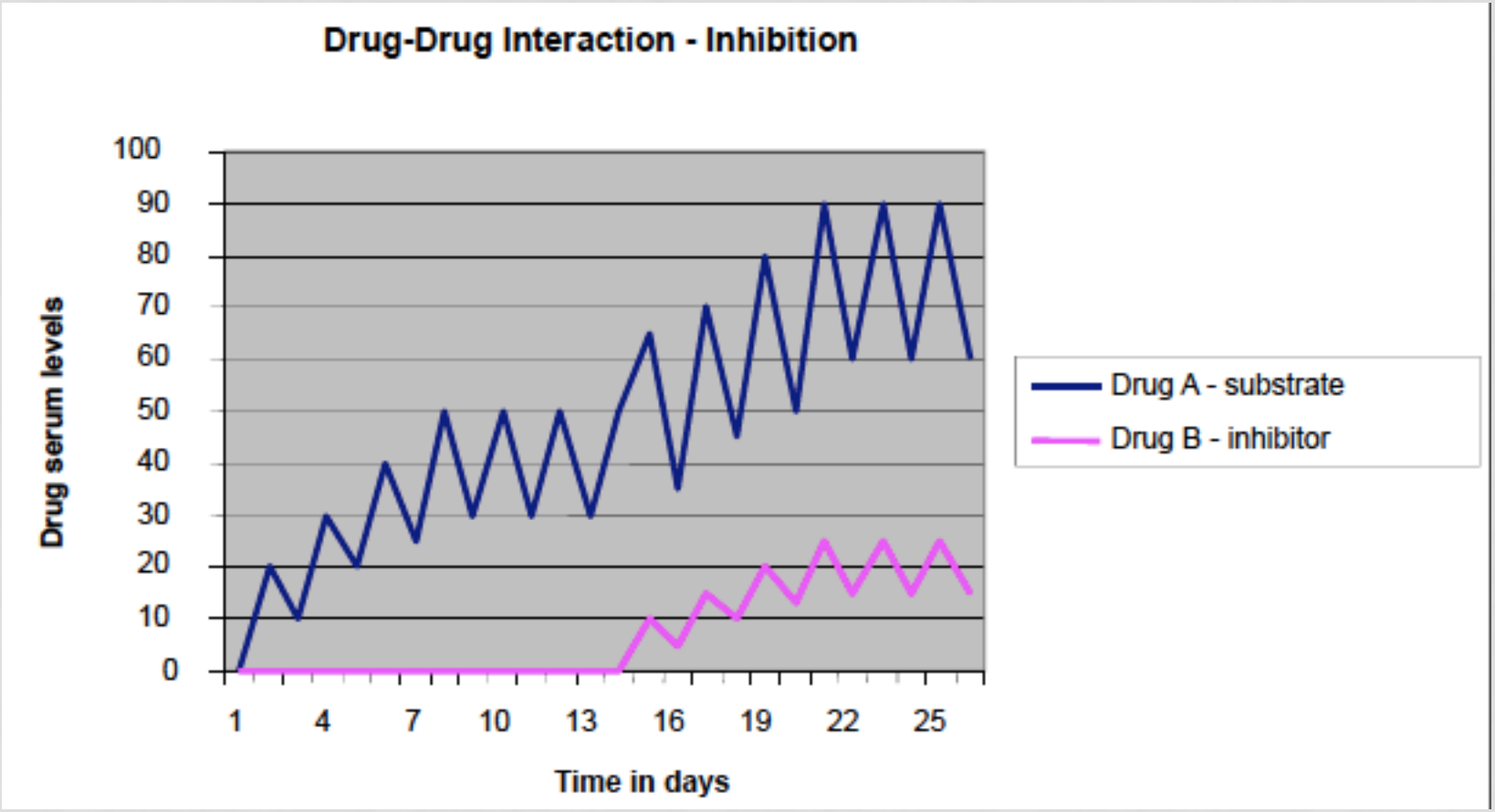


Adapted from: Wrighton SA et al. Crit Review Toxicology 1992;22:1-22.
Kashuba and Bertino. Mechanisms of drug interaction. In Drug Interactions in Infections Diseases. Humana Press. 2001.

	Substrate	Inhibitor	Inducer
3A4	***[Benzos]*** Alprazolam, Midazalam, Indinavir, Ritonavir, Saquinavir	Ketoconazole, Indinavir, ***Ritonavir***, Saquinavir, Nefazodone	Rifampicin, Carbamazepine, ***Efavirenz***, Nevirapine
2D6	Tricyclics, **[SSRI's]**, Haloperidol, Venlafaxine	Clomipramine, ***fluoxetine***, paroxetine, haloperidol, ***Ritonavir***	
2B6	Efavirenz, Nevirapine, buproprion		
2C9	Warfarin	Fluconazole	Some induction effect with 3A6 inducers

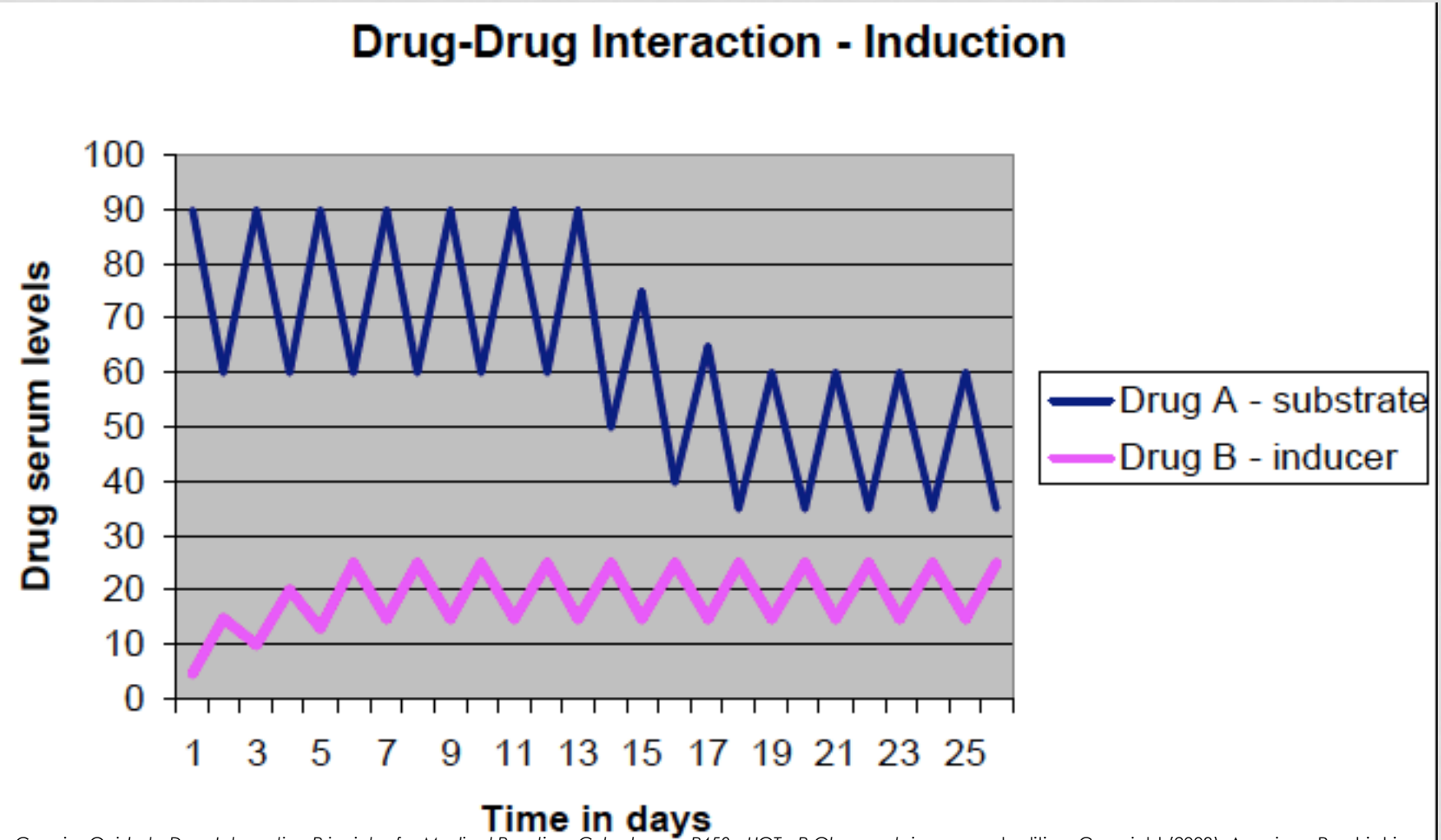
Wilkinson, NEJM, 2005

- PIs (eg: ritonavir) are mostly potent **pan-inhibitors** of CYP450 (**3A4**, 2D6, 2C9, 2C19, 2B6)



Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-Glycoproteins, second edition. Copyright (2003), American Psychiatric Press, Inc.

- NNRTI (eg: nevirapine, efavirenz) are **inducers**



Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-Glycoproteins, second edition. Copyright (2003), American Psychiatric Press, Inc.

DRUG-DRUG INTERACTIONS
CASE REPORTS

- **OLANZAPINE**
  - RTV reduced OLA by 53%, RTV CYP1A2 inducer (Penzak, 2002)
  - Fosamprenavir/ritonavir 700/100 mg b.i.d. appeared to induce olanzapine metabolism (Jacobs, 2014)
- **QUETIAPINE**
  - 57 yo man: rapid and severe weight gain when added to RTV (Pollack et al, 2009)
  - 32 yo woman: sedation and mental confusion when added to atazanavir+ritonavir (Pollack et al, 2009)
  - deep coma: 8000 mg quetiapine plus lamuvidine, ritonavir, atazanavir and tenofovir (Hantson et al, 2010)
  - priapism: with PIs (Geraci 2010, Harris et al 2006)
- **RISPERIDONE**
  - reversible coma with ritonavir (Jover et al., 2002; Kelly et al., 2002)
  - EPS and malignant syndrome with indinavir and ritonavir (Kelly et al., 2002, Lee et al., 2000)

FURTHER SUGGESTIONS

- **AMISULPRIDE**:
  - very effective in treating psychosis,
  - low rates of discontinuation
  - safer profile regarding metabolic side effects
  - minimal metabolic transformation and it does not affect CYP450→ drug-drug interaction is unlikely (Spina&Leon, 2007)
- **ASENAPINE**:
  - side effects (weight gain, EPS)
  - not recommended in hepatic impairment (Potkin, 2011)
- **PALIPERIDONE**:
  - it is not metabolized by the liver → favourable option for its lack of ARVs interaction and in HIV+ pts with comorbid liver condition

HIV Medication and Drug-Interaction Websites

- http://hivinsite.ucsf.edu/InSite
- http://www.hiv-druginteractions.org/Interactions.aspx

www.apm.org/library/monographs/hiv/index.shtml

http://www.hivclinic.ca/main/drugs_interact.html

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Welcome Update

UNIVERSITY OF LIVERPOOL

Liverpool HIV iChart

Providing summary data of HIV drug interactions. Full details available at

www.hiv-druginteractions.org

Search for Drug Interactions

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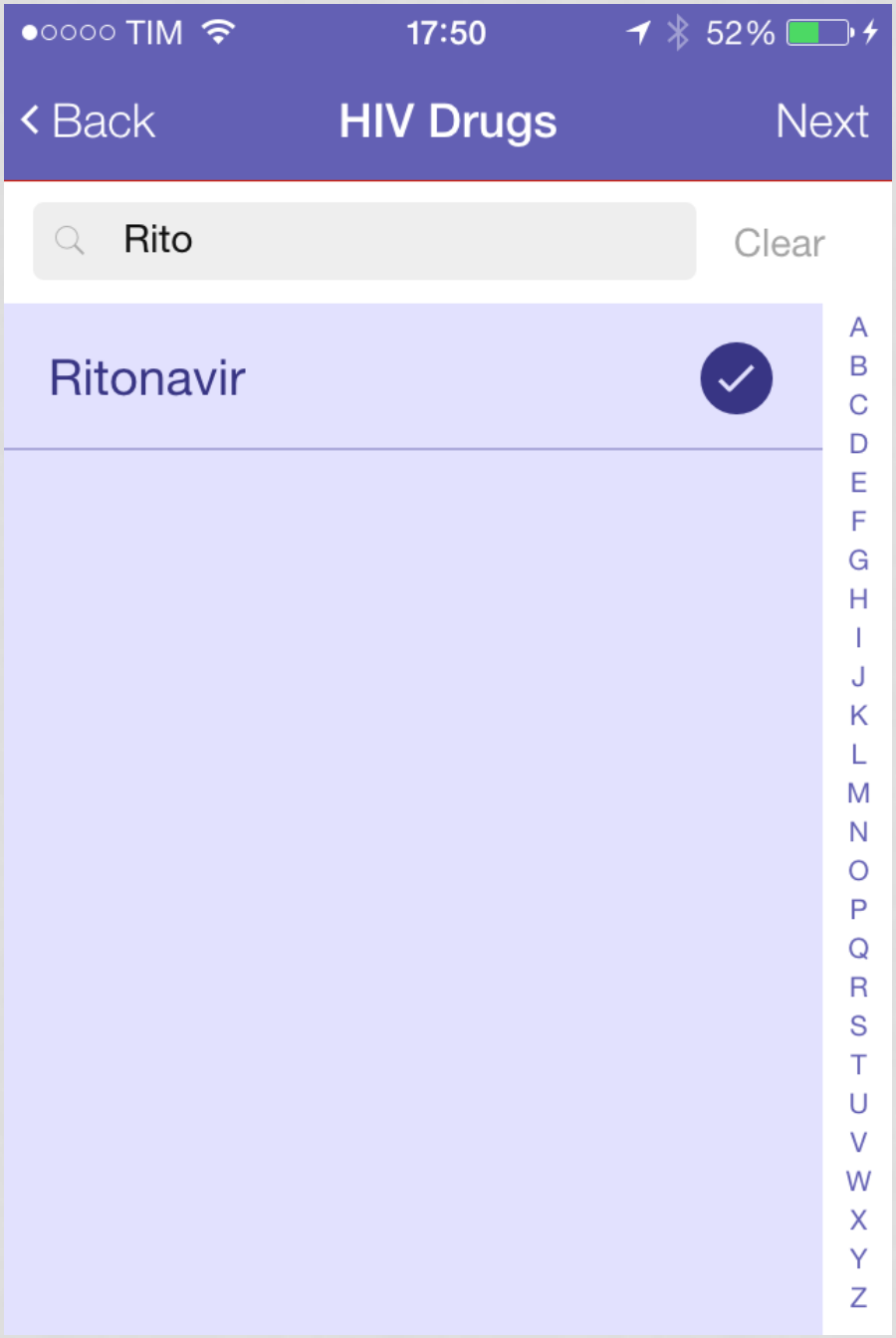
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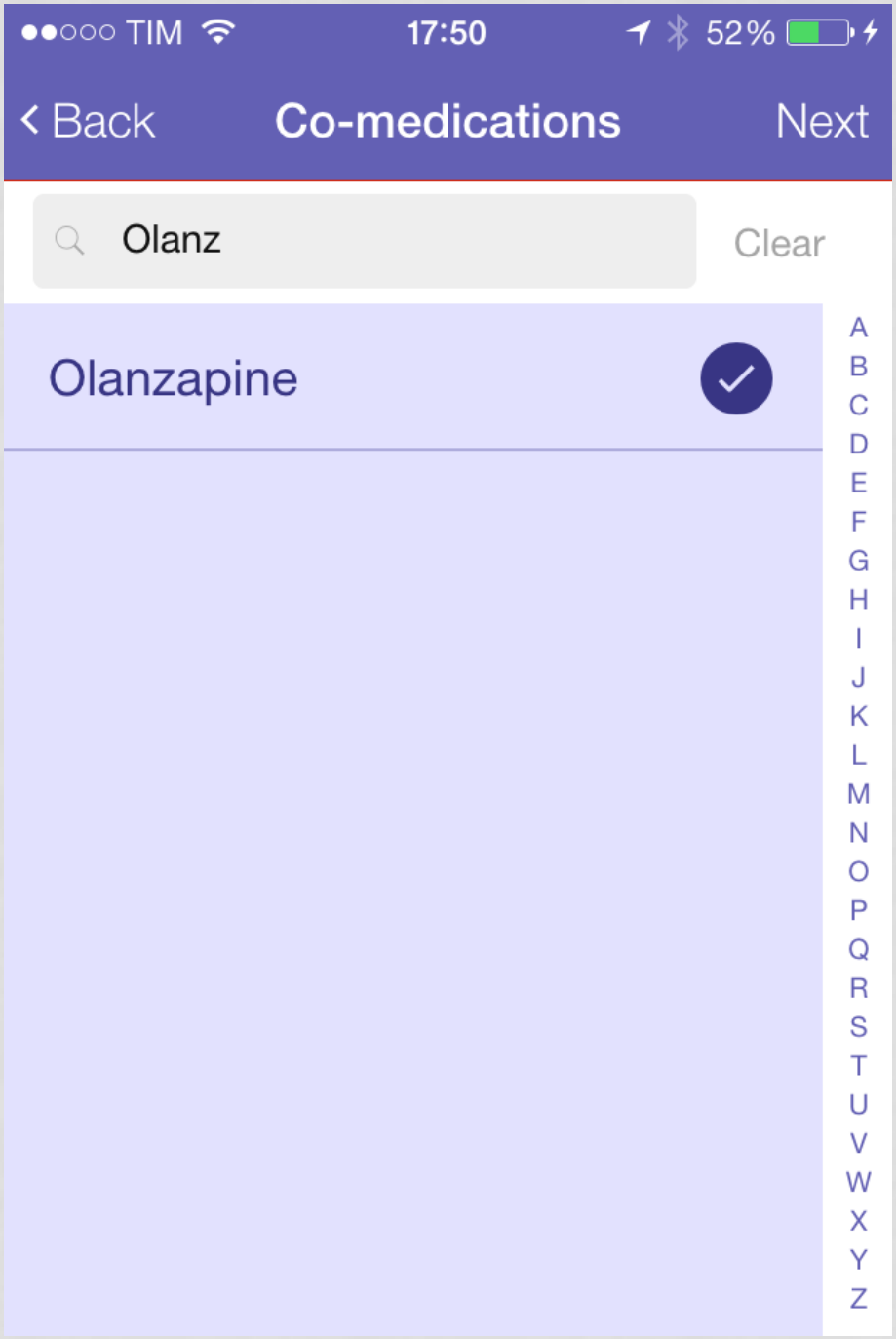
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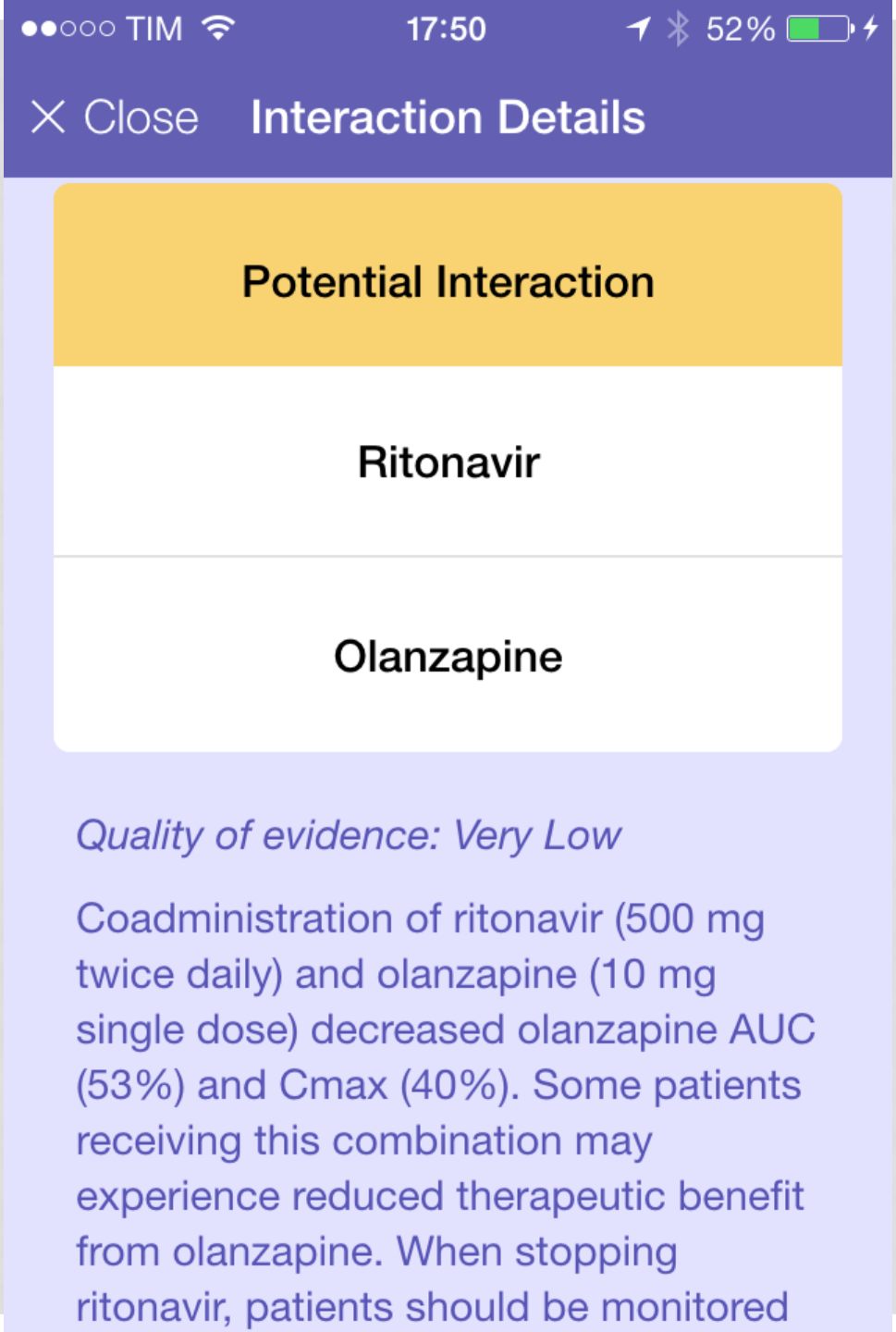
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Interaction Details
Potential Interaction
Ritonavir
Olanzapine
Quality of evidence: Very Low
Coadministration of ritonavir (500 mg twice daily) and olanzapine (10 mg single dose) decreased olanzapine AUC (53%) and Cmax (40%). Some patients receiving this combination may experience reduced therapeutic benefit from olanzapine. When stopping ritonavir, patients should be monitored

Antipsychotics	Metabolic Site(s)	Inhibits/Induces	Potential Drug–Drug Interaction with CART
Chlorpromazine	CYP2D6, 1A2, 3A4 UGT1A4, UGT1A3	Inhibits: CYP2D6	None known.
Haloperidol	CYP 2D6, 3A4, 1A2	Inhibits: CYP3A4, CYP2D6	Possible increased plasma level by PIs, reduced by NNRTI
Aripiprazole	CYP2D6, 3A4	None known	Possible increased plasma level by PIs, reduced by NNRTI
Clozapine	CYPCYP1A2, 3A4, 2D6	Inhibits: 2D6	Tenofovir. avoid in pts taking CBZ (reduced CLO leves, risk agranulocitosis)
Olanzapine	UGT 1A4 CYP 1A2, 2D6, FMO3	None	Tenofovir
		Induction of CYP 1A2 by ritonavir	Ritonavir decreases olanzapine levels
Quetiapine	CYP3A4 Sulfoxidation Oxidation P-gp substrate	None	Protease inhibitors Delavirdine Efavirenz
Risperidone	CYP 2D6, 3A4	Inhibits 2D6, 3A4	Protease inhibitors Delavirdine Efavirenz
Ziprasidone	Aldehyde oxidase CYP3A4, 1A2	None	Protease inhibitors Delavirdine Efavirenz , Tenofovir

DON'T FORGET MOOD STABILIZERS!

- **Valproic Acid (VA):**
  - rapid anti-manic effect and relatively safe broad therapeutic range.
  - it can increase liver enzymes and reduce platelets. The risk of hyperammoniemia, weight gain and teratogenicity should also be considered (R. B. Carr & Shrewsbury, 2007; Flanagan, 2008
  - Ritonavir may induce the metabolism of VA, lowering serum levels (Back, 2006).
  - VA is an enzyme inhibiting agent : it could increase serum level of lopinavir/ritonavir, zidovudine and efavirenz.
- **Carbamazepine (CBZ):**
  - CBZ is a potent pan-inducer at 3A4, 1A2 and 2C19: it has the potential to reduce serum levels of all the protease inhibitors and NNRTIs (Okulicz et al., 2013) (Baranyai et al., 2014)
  - CBZ is metabolized at many P450 enzymes, yet is subject to inhibition by pan-inhibitors such as ritonavir.
    - CBZ+RTV: vomiting, vertigo, and elevated liver enzymes with increased serum concentrations of CBZ within 12 hours of the first dose of ritonavir. (Kato et al., 2000)
- **Lithium**:
  - lithium has a favorable drug–drug interaction profile
  - careful monitoring for toxicity is essential:
    - lithium levels >1.2 mM : persistent neurological deficits (K. P. Chen, Shen, & Lu, 2004).
    - lithium levels >2.5 mEq/L: severe complications (seizures, coma, cardiac dysrhythmia, and permanent neurological impairment)

SIDE EFFECTS

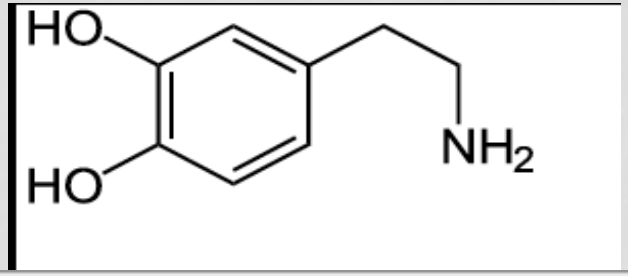
ANTIPSYCHOTICS

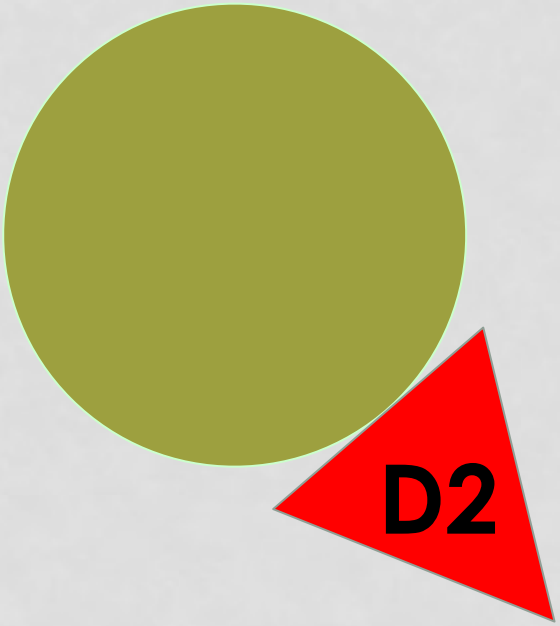
classification

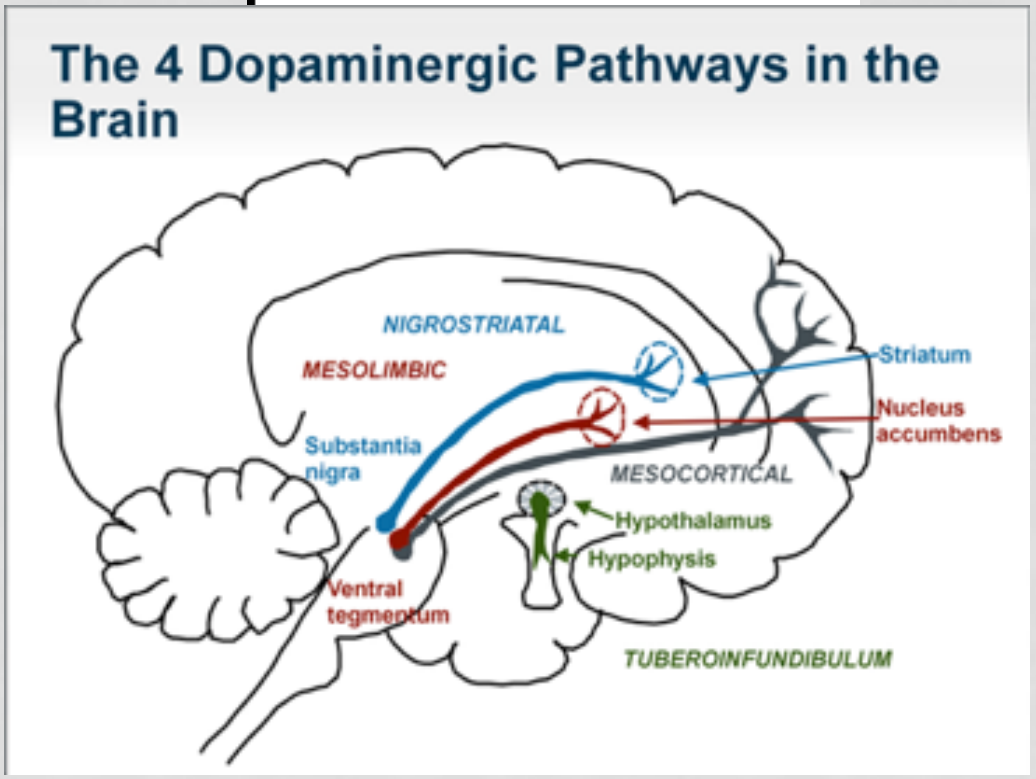
classical/
typical/
first-
generation

atypical/
second-
generation

WHAT MAKES AN ANTIPSYCHOTIC CONVENTIONAL?







WHAT MAKES AN ANTIPSYCHOTIC ATYPICAL?

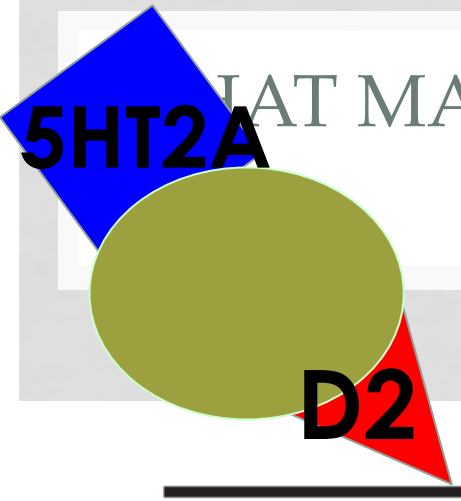


Table 2. In Vitro Receptor-Binding Profiles of the Atypical Antipsychotics[a,b]

Receptor	Clozapine (K_i, nM)	Risperidone (K_i, nM)	Olanzapine (K_i, nM)	Quetiapine (IC_{50}, nM)	Ziprasidone (K_i, nM)	Aripiprazole (K_i, nM)
D_1	85	75	31	1268	–	–
D_2	125	3	11	329	4.8	0.34
5-HT_{1A}	770	490	> 1000	717	3.4	1.7
5-HT_{1D}	980	100	800	–	2	–
5-HT_{2A}	12	0.6	4	148	0.4	3.4
5-HT_{2C}	8	26	11	–	1.3	15
α_1	7	2	19	94	10	57
H_1	6	155	7	30	47	61
M_1	1.9	> 10,000[c]	1.9	> 10,000	> 10,000[c]	> 1000[c]

[a]Data from Bristol-Myers Squibb Company,[10] Pfizer Inc.,[11] Bymaster et al.,[12] and Goldstein.[13]
[b]Dashes indicate data not presented.
[c]IC_{50}.
Abbreviations: 5-HT = serotonin, α_1 = α_1-adrenoceptor, D_1 = dopamine-1, D_2 = dopamine-2, H_1 = histamine-1, IC_{50} = concentration that inhibits 50%, K_i = inhibition constant, M_1 = muscarinic-1, nM = nanomolar.

(Prim Care Companion J Clin Psychiatry 2005;7:268–274)

SIDE EFFECTS

- **D2** (dopamine): extrapyramidal symptoms, prolactin elevation
- **M1** (muscarinic): cognitive deficits, dry mouth, constipation, urinary retention, blurred vision, increased heart rate
- **h1** (histamine): sedation, weight gain, dizziness
- **alpha-1** (a): hypotension, sedation
- **5ht2c** (serotonin): sedation, satiety blockade

Am J Psychiatry. 2006 Feb;163(2):185-94.

Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics.

Heres S[1], Davis J, Maino K, Jetzinger E, Kissling W, Leucht S.

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

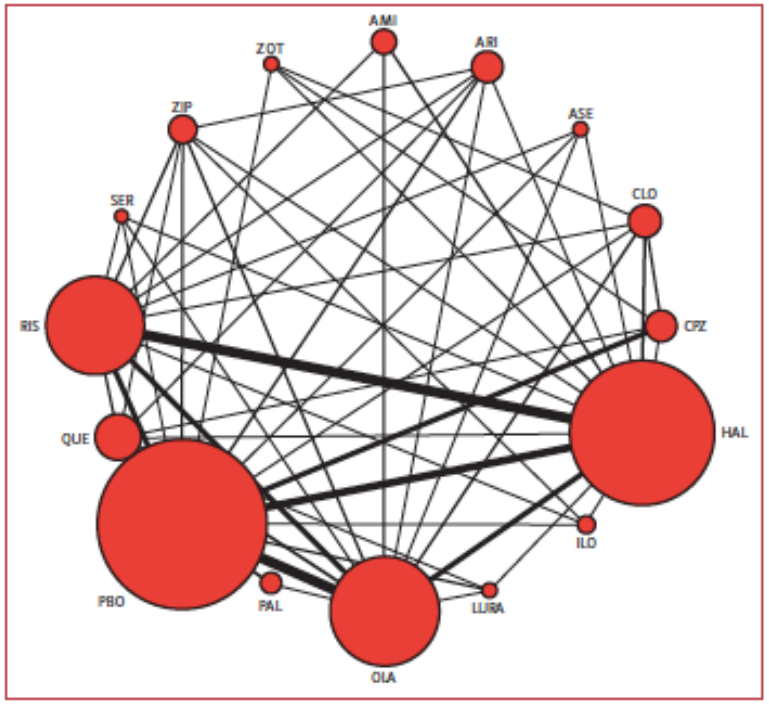
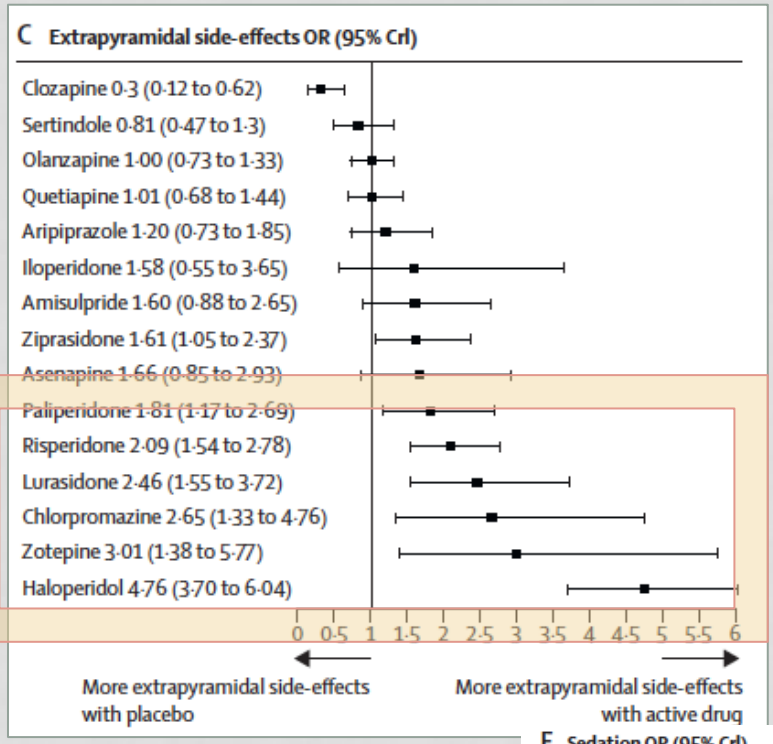
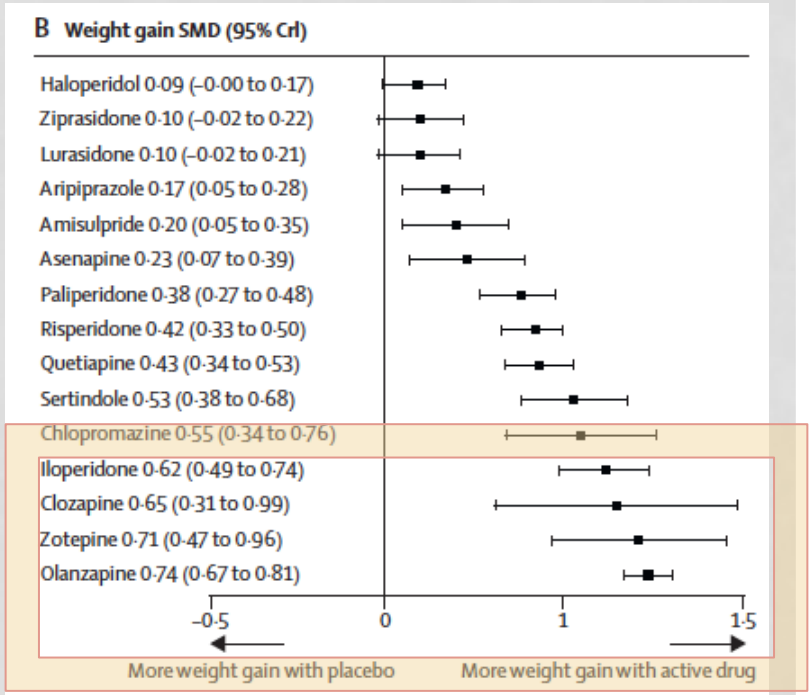
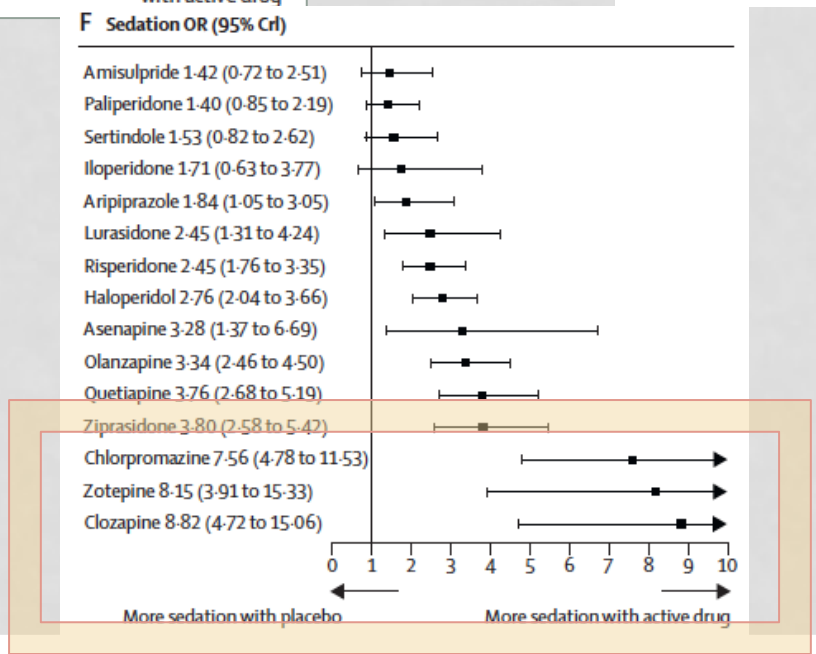


Figure 1: **Network of treatment comparisons for overall efficacy**

Lancet 2013; 382: 951–62







Lancet 2013; 382: 951–62

BJPsych | The British Journal of Psychiatry (2011)
199, 441–442. doi: 10.1192/bjp.bp.111.092718

Editorial

Physical health disparities and mental illness: the scandal of premature mortality†

Graham Thornicroft

Psychiatrists call for action over premature deaths of mentally ill

Experts say it is time to close the gap between treatment of physical and mental illnesses

JEREMY LAURANCE | Wednesday 19 June 2013

THE INDEPENDENT

PHYSICAL ILLNESSES WITH INCREASED FREQUENCY IN SMI PATIENTS

Bacterial infections and mycoses	Tuberculosis (+)
Viral diseases	HIV (++), hepatitis B/C (+)
Neoplasms	Obesity-related cancer (+)
Musculoskeletal diseases	Osteoporosis/decreased bone mineral density (+)
Stomatognathic diseases	Poor dental status (+)
Respiratory tract diseases	Impaired lung function (+)
Urological and male genital diseases	Sexual dysfunction (+)
Female genital diseases and pregnancy complications	Obstetric complications (++)
Cardiovascular diseases	Stroke, myocardial Infarction, arterial hypertension, other cardiac and vascular diseases (++)
Nutritional and metabolic diseases	Obesity (++), diabetes mellitus (+), metabolic syndrome (++), hyperlipidemia (++)

(++) very good evidence and (+) good evidence for increased risk

Adapted from Leucht et al. (Acta Psychiatr Scand 2007; 116:317-333).

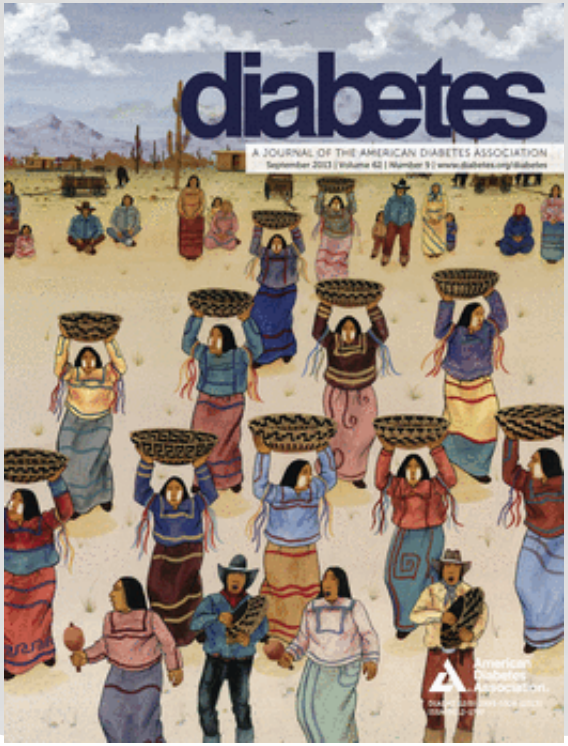
ORIGINAL ARTICLE

Antipsychotic-Induced Insulin Resistance and Postprandial Hormonal Dysregulation Independent of Weight Gain or Psychiatric Disease

Karen L. Teff,[1] Michael R. Rickels,[2] Joanna Grudziak,[1] Carissa Fuller,[2] Huong-Lan Nguyen,[1] and Karl Rickels[3]

DIABETES, VOL. 62, SEPTEMBER 2013

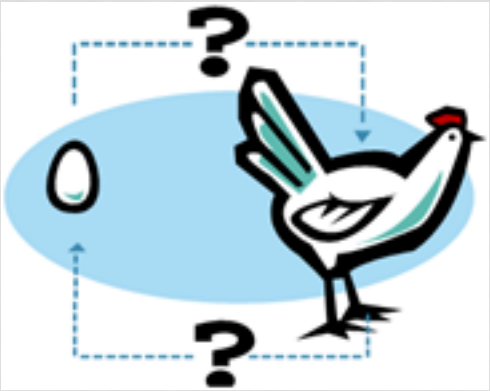
American Diabetes Association®



- **Method:** we administered olanzapine, aripiprazole, or placebo for 9 days to healthy subjects (n = 10, each group) under controlled in-patient conditions.
- **Results:** olanzapine caused significant elevations in postprandial insulin, glucagon- like peptide 1 (GLP-1), and glucagon coincident with insulin resistance compared with placebo. Aripiprazole induced insulin resistance but has no effect on postprandial hormones. Importantly, the metabolic changes occur in the absence of weight gain, increases infood intake and hunger, or psychiatric disease.
- **Hypothesis**: AAPs exert direct effects on tissues independent of mechanisms regulating eating behavior.

Some antipsychotics could bind to a **receptor X** on adipose tissue, liver and skeletal muscle – and possibly the brain – which would lead to insulin resistance.
(Stahl et al. 2009, Acta Psychiatr Scand 2009: 119:171-179)

Which comes first: atypical antipsychotic treatment or cardiometabolic risk?



S. M. Stahl[1], L. Mignon[2], J. M. Meyer[1,3]

Acta Psychiatr Scand 2009: 119: 171–179

DOI: 10.1111/j.1600-0447.2008.01334.x

DRUG-NAIVE PATIENTS

Increased visceral fat distribution in drug-naive and drug-free patients with schizophrenia

JH Thakore[1]*, JN Mann[2], I Vlahos[3], A Martin[3] and R Reznek[3]

CONCLUSION: Central obesity is a well recognized risk factor in developing certain general medical conditions. This study shows that patients with schizophrenia have increased intra-abdominal fat which may provide one explanation for why they die prematurely.

International Journal of Obesity (2002) **26**, 137–141. DOI: 10.1038/sj/ijo/0801840

Impaired Fasting Glucose Tolerance in First-Episode, Drug-Naive Patients With Schizophrenia

Conclusions: First-episode, drug-naive patients with schizophrenia have impaired fasting glucose tolerance and are more insulin resistant and have higher levels of plasma glucose, insulin, and cortisol than healthy comparison subjects.

(Am J Psychiatry 2003; 160:284–289)

Impaired glucose tolerance in first-episode drug-naïve patients with schizophrenia

L. M. Spelman, P. I. Walsh, N. Sharifi*, P. Collinst and J. H. Thakore

Conclusions The high point prevalence of IGT in never-treated patients and relatives supports either shared environmental or genetic predisposition to IGT. Both patients and their relatives present an ideal cost-effective opportunity to screen for Type 2 diabetes mellitus, as they are both easily identifiable.

Diabet. Med. 24, 481–485 (2007)

Insulin and Insulin-Like Growth Factor-1 Abnormalities in Antipsychotic-Naive Schizophrenia

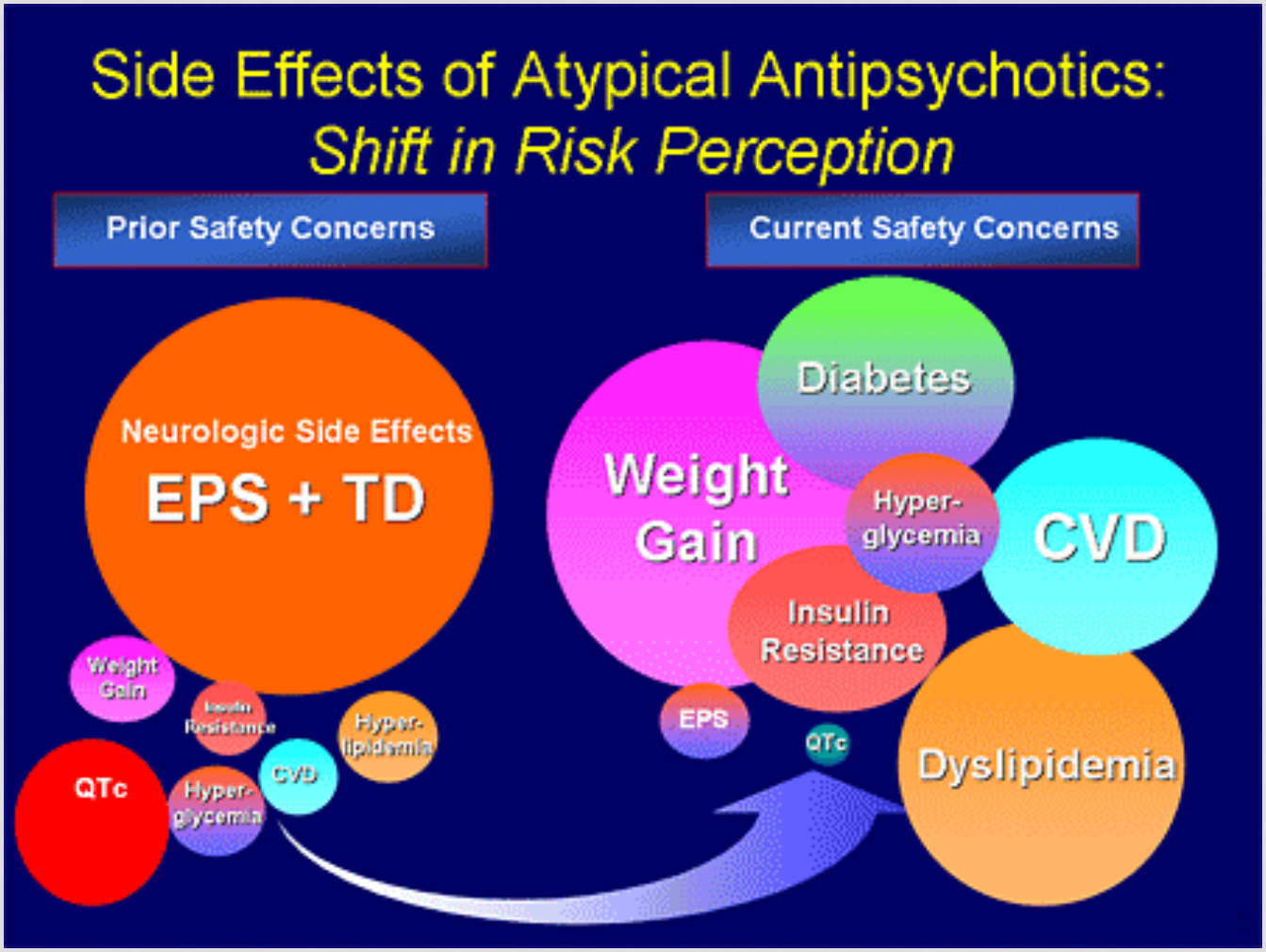
Schizophrenia patients had a significantly higher mean plasma insulin level as well as a significantly higher mean insulin resistance score relative to healthy comparison subjects.

(Am J Psychiatry 2007; 164:1557–1560)

168th meeting of the American Psychiatric Association.

- Data analysis revealed that the best predictor of long-term weight gain was a gain of more than 5% of the patient's weight after one month. After one month if the patient gained more than 5% of weight he or she is more likely to gain 15% of weight after three months and more than 20% at 12 months, according **to Dr. Eap.**
- they genotyped patients for genes related to BMI, diabetes, and other candidate genes and associated the genetic data with clinical data.
- They found that relying on clinical data alone lead to 17% accuracy in predicting weight gain, while incorporating data from genes related to BMI and candidate genes lead to 87% accuracy.

Metabolic abnormalities in patients with SMI



Metabolic abnormalities in HIV adults taking ARVs

1990

2015

- cART has markedly reduced the mortality due to HIV but has also led to an increase in metabolic and anthropomorphic side effects [Carr, 1998; Falutz, 2007, Germinario, 2003; Nolan, 2003]
- Protease Inhibitors are linked to insulin resistance, dyslipidemia and central fat hypertrophy, through increased mitochondrial oxidative stress
- Thymidine Analogues mainly promote lipoatrophy, which could result from mitochondrial toxicity and adipocyte apoptosis [Lagathu C., 2007]
- The prevalence of MetS in HIV infected people ranges from 25 to 96% depending on the definition in use [Carr, 1999; Fantoni, 2002]

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Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

The concomitant use of second-generation antipsychotics and long-term antiretroviral therapy may be associated with increased cardiovascular risk

Maria Ferrara [a,b,*], Anya Umlauf [b], Chelsea Sanders [b], Jonathan M. Meyer [c,d], John Allen McCutchan [b], Nichole Duarte [b], Joseph Hampton Atkinson [d,b], Igor Grant [b], Ronald J. Ellis [b], the CHARTER Group

after controlling for demographic and HIV disease- and ART-related covariates. Of 2229 HIV-infected participants, 12% ($N=258$) were treated with SGAs. In multivariable models adjusted for relevant covariates, the SGA+ group had significantly higher mean triglycerides, significantly higher odds of DM, significantly higher MAPs and marginally higher BMI. The use of SGAs in HIV-infected adults taking ART was independently associated with worse indicators of MetS and cardiovascular risk. Aggressive monitoring for the metabolic complications from concurrent SGA and ART is indicated in all patients receiving these medication combinations.

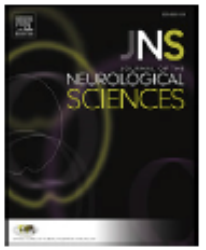
(UN)EXPECTED SIDE EFFECTS OF SIDE EFFECTS

Journal of the Neurological Sciences 351 (2015) 18–23

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns



The metabolic syndrome in a memory clinic population: Relation with clinical profile and prognosis

Lieza G. Exalto [b,i,*], Wiesje M. van der Flier [c,i], Caroline J.M. van Boheemen [d], L. Jaap Kappelle [b], Hugo Vrenken [e,f,i], Charlotte Teunissen [g,i], Ted Koene [h,i], Phillip Scheltens [a,i], Geert Jan Biessels [b]

Among non demented patients presenting at a memory clinic, MetS was associated with slightly worse cognitive performance (worse on tasks assessing executive functions, visuo-constructive ability, attention & speed), but conversion rate to dementia was not increased.

ORIGINAL ARTICLE

OMAN MEDICAL JOURNAL [2015], VOL. 30, NO. 2: 100–103

The Metabolic Syndrome and Inflammation: Role of Insulin Resistance and Increased Adiposity

Wajiha Farooq[1]*, Umme Farwa[1] and Faisal Rashid Khan[2]

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[2]Al Nafees Medical and Dental college, Islamabad, Pakistan

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Keywords:
Metabolic Syndrome; Inflammation; Insulin Resistance; Obesity.

ABSTRACT

Objectives: We sought to determine the role of obesity and insulin resistance (IR) in the pathogenesis of inflammation in metabolic syndrome (MetS). ***Methods:*** Our study included 100 patients with MetS and 100 age and gender matched control patients who attended a tertiary care laboratory in Rawalpindi, Pakistan. Anthropometric data was obtained including height and weight to calculate body mass index. A record of patient's blood pressure (BP), waist circumference (WC) and hip circumference (HC) was made. Biochemical analysis included measurements of fasting glucose, triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), insulin, and high-sensitivity C reactive protein (hsCRP). IR was determined by the homeostasis mode assessment insulin resistance (HOMA-IR) method. ***Results:*** The levels of hs-CRP were found to be elevated in all patients with MetS where it correlated significantly with all its components including measures of obesity, fasting insulin and glucose levels, IR, TG and HDL-c. However, on linear regression analysis only WC, fasting insulin, and HOMA-IR remained significantly correlated with hs-CRP. ***Conclusion:*** MetS is a condition characterized by chronic low-grade inflammation, which arises because of increased abdominal adiposity and IR. Large multicenter studies are needed to gain insight into its pathogenesis and derive treatment strategies.

Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome

Bhumsoo Kim and Eva L Feldman

Experimental & Molecular Medicine (2015) 47, e149; doi:10.1038/emm.2015.3

www.nature.com/emm

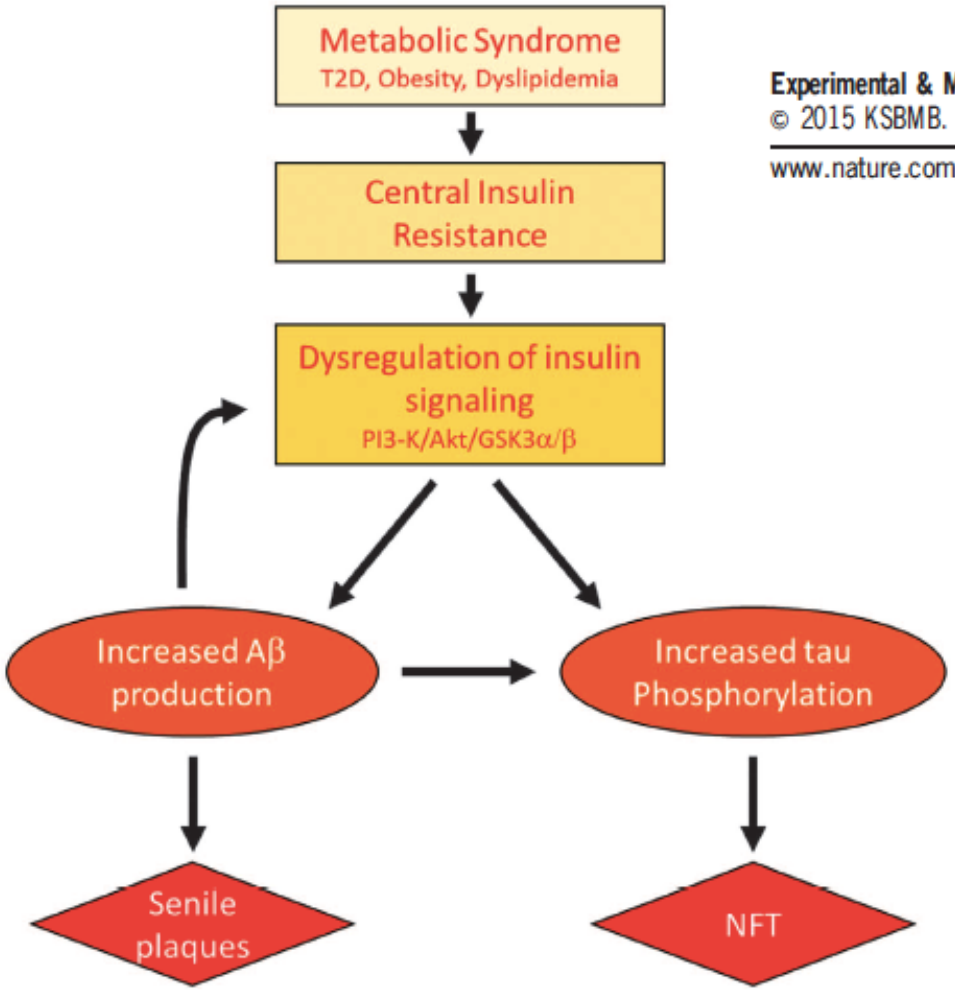


Figure 1 MetS and AD Aβ/tau pathology may act in a feed-forward mechanism to accelerate AD pathology in the presence of IR.

Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder

RESULTS:

- obesity, and WC, but not BMI, were associated with NCI.
- Self-reported diabetes was associated with NCI in the substudy and in those 55 in the entire CHARTER cohort.
- Multivariate logistic regression analyses demonstrated that central obesity increased the risk of NCI

McCutchan JA, Marquie-Beck JA, Fitzsimons CA, Letendre SL, Ellis RJ, Heaton RK, Wolfson T, Rosario D, Alexander TJ, Marra C, Ances BM, Grant I; CHARTER Group. Neurology. 2012 Feb 14;78(7):485-92

Abdominal Obesity Contributes to Neurocognitive Impairment in HIV-Infected Patients With Increased Inflammation and Immune Activation

Fred R. Sattler, MD, Jiaxiu He, PhD,† Scott Letendre, MD,‡ Cara Wilson, MD,¶ Chelsea Sanders, MS,‡ Robert Heaton, PhD,§ Ronald Ellis, MD,‖ Donald Franklin, PhD,§ Grace Aldrovandi, MD,# Christina M. Marra, MD,** David Clifford, MD,†† Susan Morgello, MD,‡‡ Igor Grant, MD,§ and J. Allen McCutchan, MD, MSc,‡ for the CHARTER Group*

Participants: One hundred fifty-two patients with plasma HIV RNA <1000 copies per milliliter had clinical evaluations and cognitive function quantified by global deficit scores (GDS).

RESULTS:

1) WC and plasma IL-6 levels positively correlated with GDS
2) in the high tertile of CSF sCD40L (biomarker of macrophage and microglial activation), the correlation of IL-6 with GDS was strongest
3) NCI was more common for individuals with components of the metabolic syndrome

Human immunodeficiency virus (HIV) modulates the associations between insulin resistance and cognition in the current combination antiretroviral therapy (cART) era: a study of the Women's Interagency HIV Study (WIHS)

Victor Valcour · Leah H. Rubin · Phyllis Tien · Kathryn Anastos · Mary Young · Wendy Mack · Mardge Cohen · Elizabeth T. Golub · Howard Crystal · Pauline M. Maki

This study examined IR among non-diabetics in relation to a 1-h neuropsychological test battery among 994 women (659 HIV-infected and 335 HIV-uninfected controls) assessed.

1) increasing HOMA was significantly associated with reduced performance on Letter-Number Sequencing (LNS) attention task and on Hopkins Verbal Learning Test (HVLT) recognition with weaker but statistically significant associations on phonemic fluency.
2) An HIV*HOMA interaction effect was identified on the LNS attention task and Stroop trials 1 and 2, with worse performance in HIV-infected
3) cohort members who had diabetes mellitus performed worse on the grooved pegboard test of psychomotor speed and manual dexterity.

Brain morphometric correlates of metabolic variables in HIV: the CHARTER study

S. L. Archibald · J. A. McCutchan · C. Sanders · T. Wolfson · T. L. Jernigan · R. J. Ellis · B. M. Ances · A. C. Collier · J. C. McArthur · S. Morgello · D. M. Simpson · C. Marra · B. B. Gelman · D. B. Clifford · I. Grant · C. Fennema-Notestine · for the CHARTER Group

1) Greater BMI was associated with smaller cortical gray and larger white matter volumes.
2) Higher total cholesterol (C) levels were associated with smaller cortex volumes;
3) higher LDL-C was associated with larger cerebral white matter volumes
4) higher HDL-C levels were associated with larger sulci;
5) Higher blood glucose levels diabetes were associated with more abnormal white matter.

U.S. Psychiatric and Mental Health Congress

18 maggio alle ore 15.50 ·

News from APA 2015:

Can Hyperlipidemia Improve Negative Symptoms of Schizophrenia?

Read more here: http://bit.ly/1dffTha

Mi piace · Commenta · Condividi

HYPERLIPIDEMIA:
BAD FOR THE HEART, GOOD FOR THE BRAIN?

Elevated Cholesterol and Triglycerides are Associated with Better Cognitive Functioning in Schizophrenia Data From the CATIE Study.

Nasrallah H. Poster presented at the 168th meeting of the APA. **16 May 2015.**

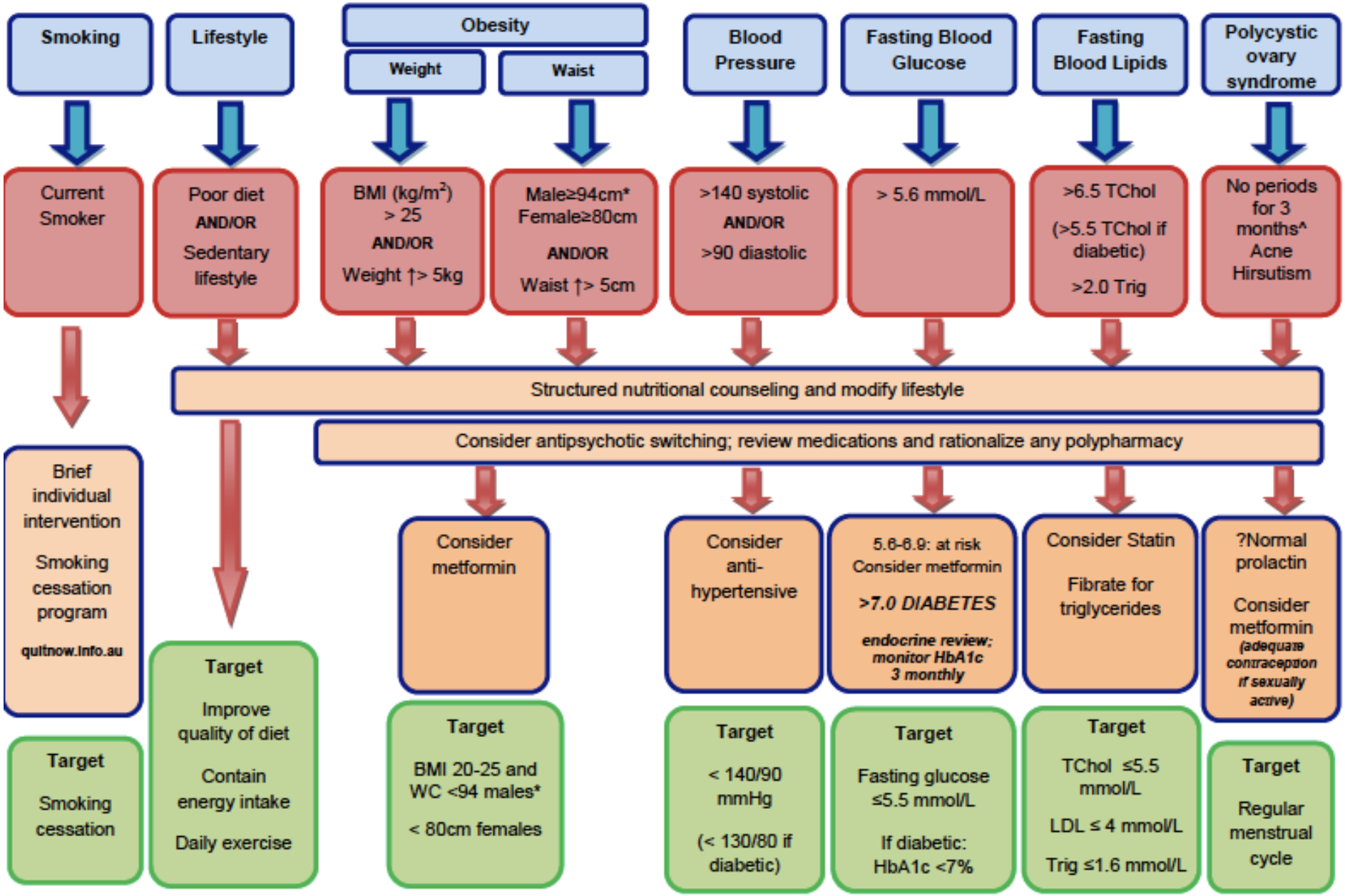
- high cholesterol and high tryglicerides associated to better neurocognition scores.
- people with low HDL scores fared worse on neurocognitive measures than people with high HDL scores.
- **HYPOTHESIS**: higher lipids in cell membranes and myelin→ better conduction of signal in CNS→ better cognition

"We psychiatrists are caught in a bind. High lipids increase cardiovascular mortality, but high lipids are also associated with better cognition. And there is no treatment for cognition in schizophrenia. It's a big challenge, a huge unmet need,"

INTERVENTIONS


Medical Risk Management Strategies in Antipsychotic-Treated Patients
PREVENTION
PRIMARY
Treatment Initiation
• Healthy lifestyle counseling
• Healthy lifestyle intervention
• Start with lower-risk antipsychotic
SECONDARY
If Adverse Effect Is Present
• Healthy lifestyle counseling/intervention
• Consider changing to lower-risk antipsychotic
• Consider weight loss intervention
TERTIARY
If Adverse Effect Progresses/Serious
• Healthy lifestyle counseling/intervention
• Considering changing to lower-risk antipsychotic
• Add targeted treatment for pathological values
• Consider referral to specialist
Correll CU. CNS Spectr. Vol 12. No 10 (Suppl 17), 2007: 12-20,35.

Positive Cardiometabolic Health : an early intervention framework for patients on psychotropic medication



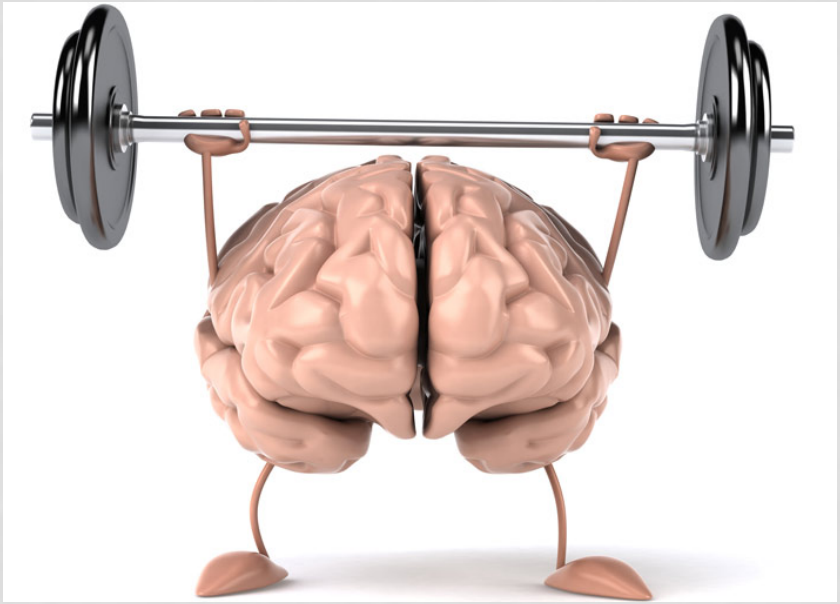
Curtis J, Newall H, Samaras K. HETI 2011

* for south Asians, Chinese, south and central American and Japanese individuals, recommend WC target < 90cm

^ for premenopausal women

WHAT'S NEXT

- **correlation** between metabolic side effects and NCI
- need more **RCTs** for newer HIV drugs and newer antipsychotics
- **interventions**: when? how? with what? (metformin, statins, ASA, switch antipsychotic)



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Physical Exercise is Associated with Less Neurocognitive Impairment Among HIV-Infected Adults

Ms Catherine A. Dufour[1], Dr Maria J. Marquine[1], Dr Pariya L. Fazeli[1], Dr Brook L. Henry[1], Dr Ronald J. Ellis[2], Dr Igor Grant[1], David J. Moore[1], and the HNRP Group

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Experimental Gerontology

Volume 46, Issues 2–3, February–March 2011, Pages 112–115

Proceeding of the Tenth International Symposium on Neurobiology and Neuroendocrinology of Aging

Intranasal insulin as a therapeutic option in the treatment of cognitive impairments

Christian Benedict[a, b], William H. Frey II[c], Helgi B. Schiöth[a], Bernd Schultes[d], Jan Born[b], Manfred Hallschmid[b]

- Intranasal insulin, however, is only effective in early AD and MCI patients, and individuals with the ApoEε 4 allele do not respond well.
- Given the current obesity epidemic among all ages and increased life expectancy, there is a critical need to understand the underlying causes of cognitive impairment due to IR, which may be the key link for the increased incidence of AD.

CONCLUSIONS

- start slow and go slow
- avoid complex regimens
- remove meds whenever possible
- anticipate drug interactions
- avoid toxic meds with narrow therapeutic windows

Gallego L. et al, AIDS Rev. 2012 Apr-Jun;14(2):101-11.
Repetto MJ et al, Psychosom Med. 2008 Jun;70(5):585-92
Watkins CC et al., Drug Saf. 2011 Aug 1;34(8):623-39.
THE MAUDSLEY PRESCRIBING GUIDELINES IN PSYCHIATRY, 2015

CONCLUSIONS

- early monitoring on weight gain and other metabolic disturbances [olanzapine, clozapine, risperidone];
- **AVOID**: viral breakthrough and development of resistance, sub-optimal disease/symptom management, drug toxicity and possible non-adherence due to excessive side effects;
- must take into account side effect profile of the drug, clinical drug-drug interactions, cost, patient preference and history of patient medication response.

¡GRACIAS!

maria.ferrara@live.it