CONGRESSO REGIONALE
AMD-SID LAZIO

Il Diabete e gli Psicofarmaci

V. Fiore

UOSD Diabetologia ed Endocrinologia
ASL RM5

CONGRESSO REGIONALE
AMD-SID LAZIO

Il /la dr./sa Vincenzo Fiore dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche (tramite provider):

- Novo N, Lilly, Sanofi, Merck, Bayer, Astra Z., Novartis, Menarini, Roche,

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Psicofarmaci

agiscono a livello del sistema nervoso centrale, stimolando il rilascio di diversi tipi di **neurotrasmettitori**

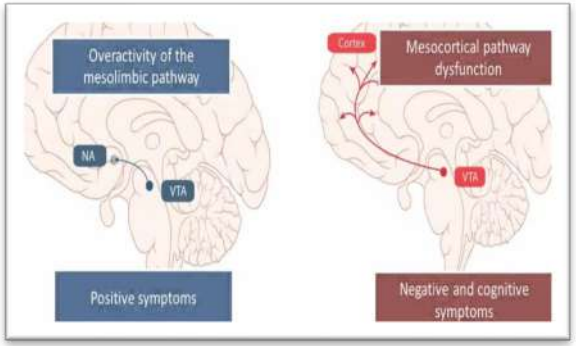
- Antipsicotici
- Antidepressivi
- Stabilizzatori dell'umore
- Ansiolitici

Farmaci Antipsicotici

>> antipsicotici agisce sulla *trasmissione dopaminergica*
(*razionale per la teoria dopaminergica come base organica della schizofrenia*).

•**Antipsicotici tipici** (o di prima generazione, anni 50-60)
✓clorpromazina, aloperidolo

Efficaci soprattutto sui sintomi negativi, meno sui positivi
Danno sindrome extra-piramidale



•**Antipsicotici atipici** (o di seconda generazione)
✓Olanzapina, Quetiapina, Risperidone, Aripiprazolo

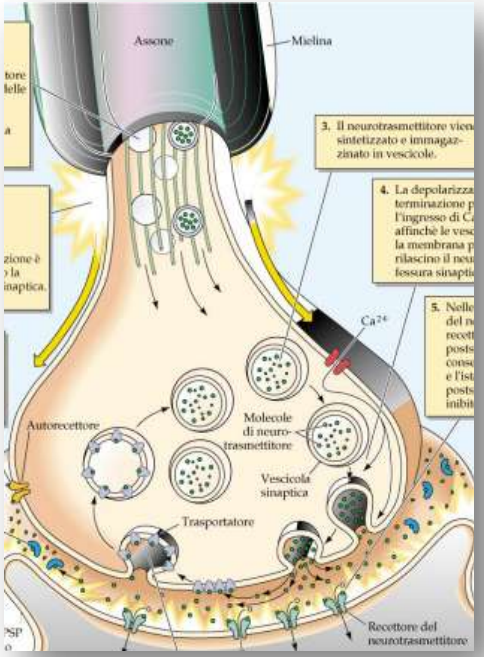
Molto più efficaci nel controllare i sintomi positivi, ridotto rischio di effetti extra-piramidali.

Farmaci Antidepressivi

Ipotesi sull'origine della depressione*:*
Riduzione funzionale della trasmissione monoaminergica

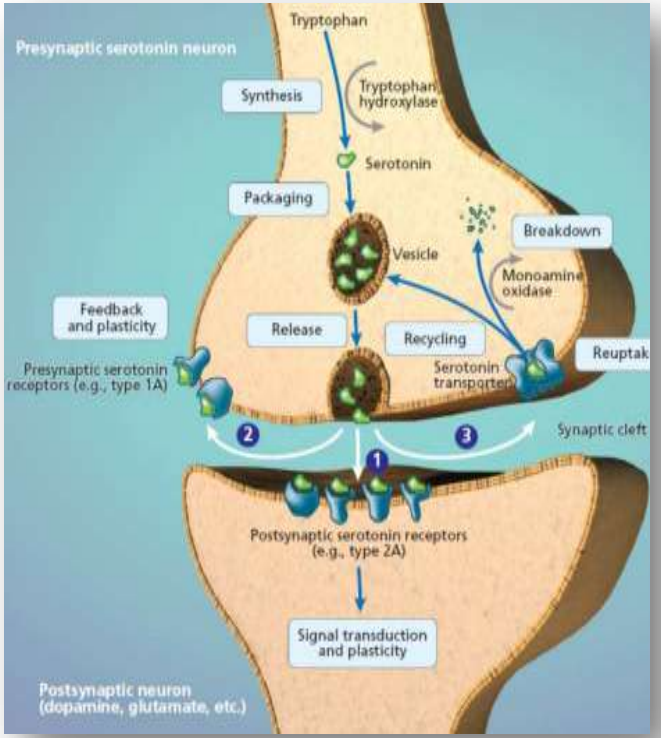
- ↓ dei *neurotrasmettitori* monoaminergici **(Na, Ser o 5-HT, DA)** *sp.intersinaptico*
- ↓ dei *recettori monoaminergici postsinaptici* che mediano la risposta biologica
- "Up-regulation" degli autorecettori monoaminergici *presinaptici* che controllano il rilascio delle monoamine

Tutti i farmaci antidepressivi agiscono **aumentando i livelli di monoamine nella terminazione sinaptica**



Farmaci Antidepressivi (prima generazione)

Blocco della ricaptazione di monoamine (aumenta la concentrazione di neurotrasmettitori nello spazio intersinaptico).



- **Inibitori selettivi delle MAO** *(monoaminossidasi)*

  ↑ dei livelli di neurotrasmettitori nello spazio sinaptico

  a. **Irreversibili: tranilcipromina, selegilina (MAO B)**
  b. **Reversibili: moclobemide, MAO A**

- **a. Inibitori Non selettivi (NA, 5-HT, DA)**
  Antidepressivi triciclici (TCA), es. Amitriptilina, Imipramina, Clorimipramina, Nortriptilina

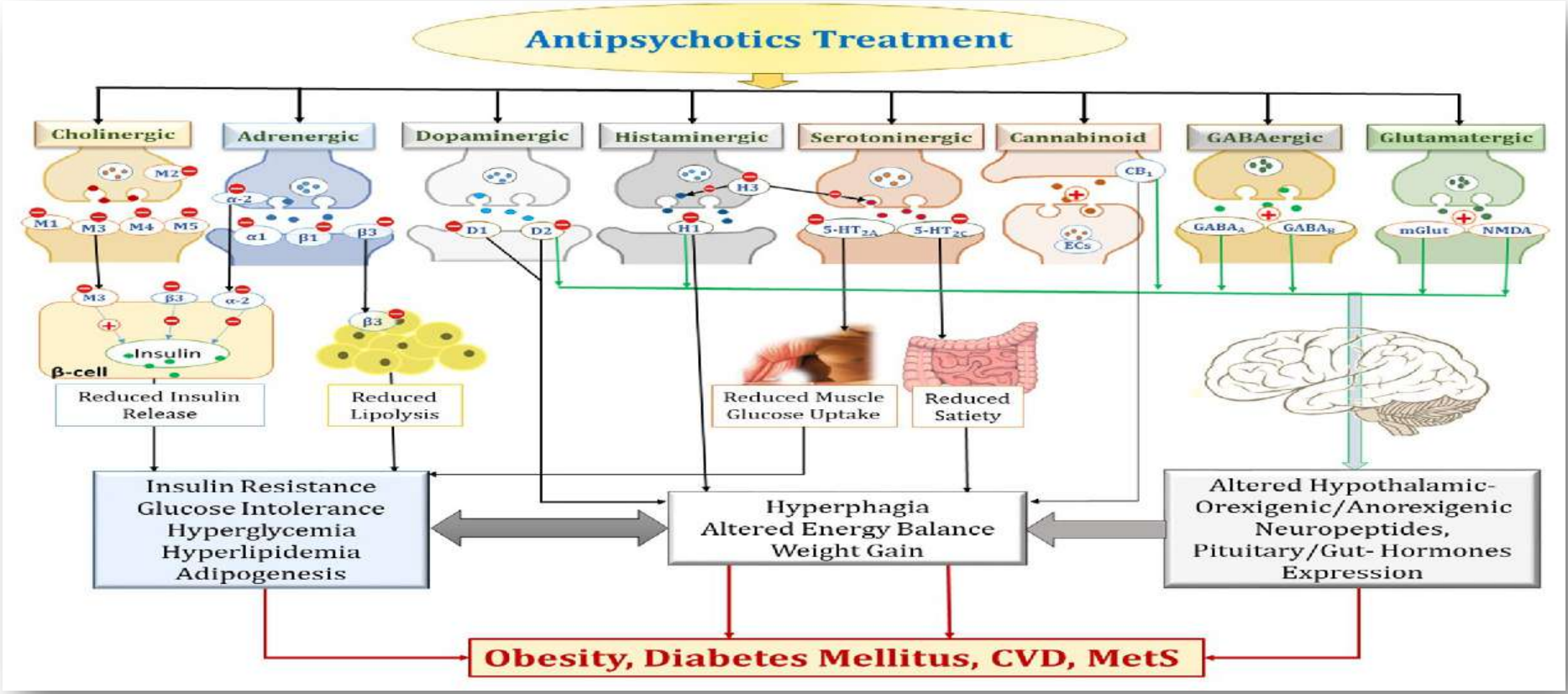
Farmaci Antidepressivi (seconda generazione)

Classe farmacologica	Principali principi attivi
Inibitori selettivi ricaptazione serotonina (SSRI)	citalopram; escitalopram; fluoxetina; fluvoxamina; paroxetina; sertralina, ecc
Inibitori selettivi ricaptazione noradrenalina (NARI)	reboxetina
Inibitori ricaptazione serotonina e noradrenalina (SNRI)	enlafaxina; duloxetina
Inibitori ricaptazione noradrenalina e dopamina (NDRI)	bupropione
Antidepressivi noradrenergici e serotoninergici specifici (NaSSA)	Mianserina; mirtazapina.
Antidepressivi ad azione serotoninergica mista (SARI)	trazodone; nefazodone.
Agonisti melatoninergici	agomelatina

CONGRESSO REGIONALE
AMD-SID LAZIO

what are the causes that favor the onset of diabetes during Antipsychotic Therapy?

Schematic Representation of Interaction of AAPs with Major Neurotransmitter-Receptors and association with Metabolic Alterations



R. Singh. European Journal of Pharmacology 844 (2019) 231–240

A Double Blind, Placebo-Controlled, Randomized Crossover Study of the Acute Metabolic Effects of Olanzapine in Healthy Volunteers

Vance L. Albaugh[1], Ravi Singareddy[2], David Mauger[3], Christopher J. Lynch[1]*

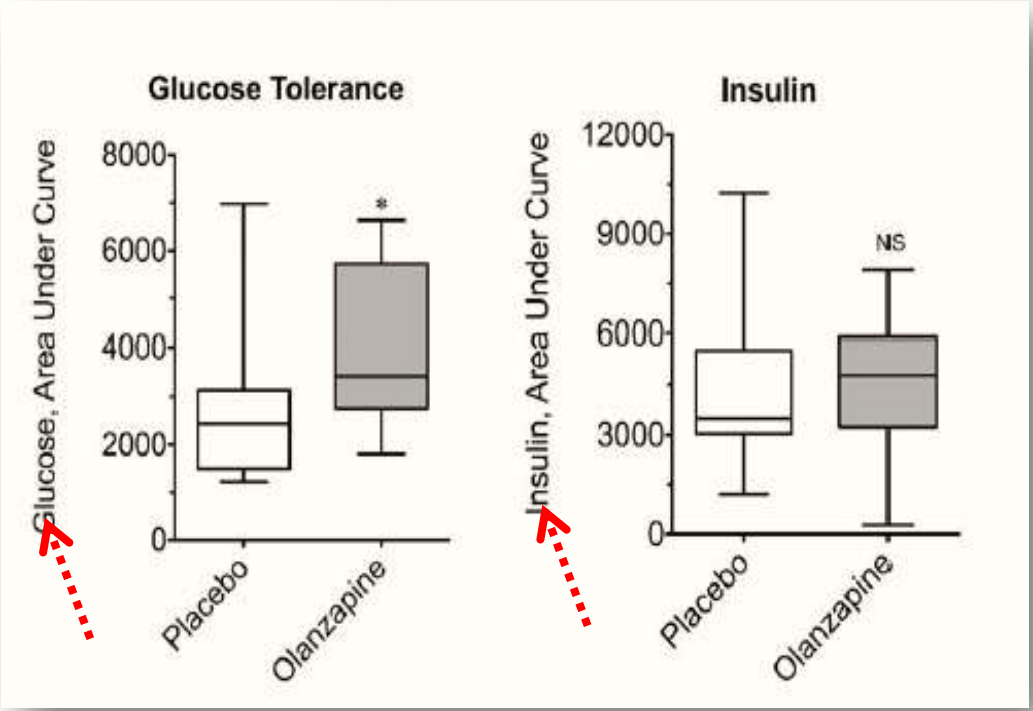
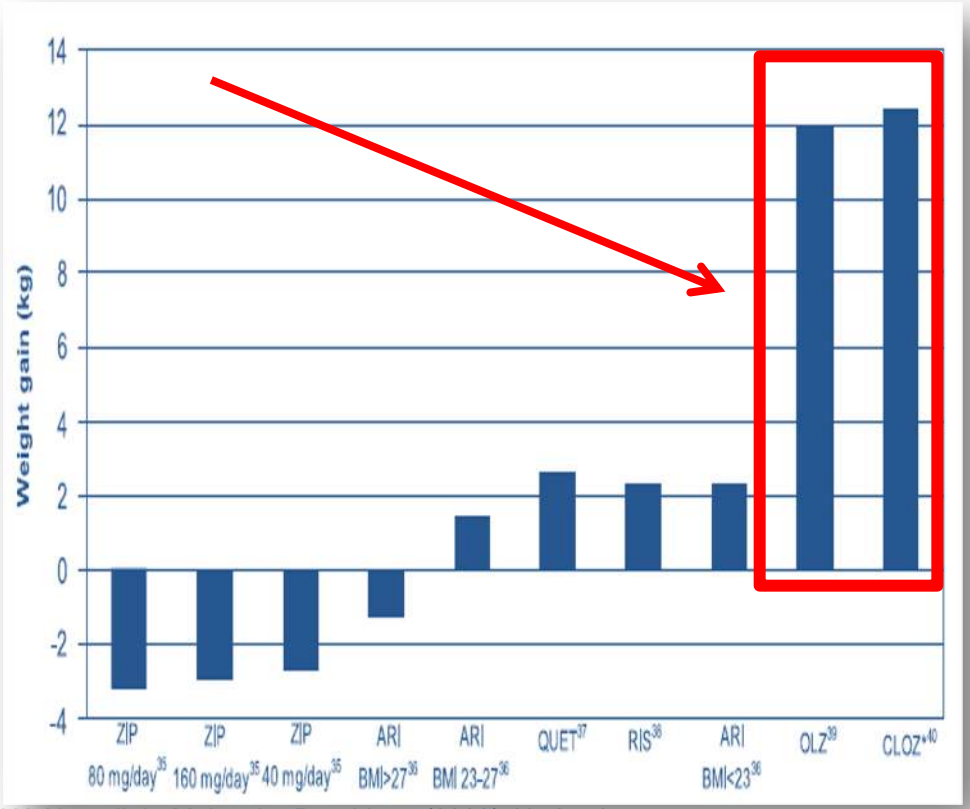


Figure 3. Effects of olanzapine on the glucose and insulin responses during oral glucose challenge. Blinded olanzapine or placebo tablets were self-administered by healthy volunteers for three days prior to conduction of a standard oral glucose tolerance test. In the morning, approximately 10–12 h following the final dose of placebo or drug compound, baseline blood samples were collected and then volunteers self-administered an oral glucose-containing solution. Serial blood samples were drawn at 30 min intervals for two hours. Plasma glucose and insulin concentrations were determined for each time point of the tolerance test. Area under the curve for (A) Glucose and (B) Insulin were calculated for each individual oral glucose tolerance test under placebo and active drug conditions. Data are expressed as box

Altered glucose homeostasis developed **after certain hours-days** of AAPs treatment **which is independent of weight gain** in both rodents and human

One-year Weight Gain in Patients Treated with Atypical Antipsychotics



HA Nasrallah, Molecular Psychiatry (2008) 13, 27–35

Risk of weight gain associated with second-generation antipsychotics

Table 1 Risk of weight gain associated with second-generation antipsychotics [8, 15, 16]

Antipsychotic	Risk of weight gain
Aripiprazole	Low
Brexpiprazole	Low
Cariprazine	Low
Lurasidone	Low
Ziprasidone	Low
Amisulpride	Intermediate
Asenapine	Intermediate
Quetiapine	Intermediate
Risperidone	Intermediate
Paliperidone	Intermediate
Iloperidone	Intermediate
Sertindole	High
Zotepine	High
Clozapine	High
Olanzapine	High

Simona Cernea, Drugs. 2020

Receptor-Binding Profile and Metabolic Risk of Antipsychotic Drugs

	RECEPTOR BINDING PROFILE																					RISK		
	D_1	D_2	D_3	D_4	H_1	H_2	H_3	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_6	5-HT_7	M_1	M_3	α_1	α_{2A}	α_{2B}	α_{2C}	Transporter	Weight Gain	Glucose Abn	Lipid Abn
Olanzapine	++	++	++	++	+++	++	+		+	+++	++	++	+++	++	++	++	++	+	++	++		++++	++	++
Zotepine	++	+++	+++	+	+++	+		+	++	+++		+++	+++	++	+	+	+++	+	+++	++	SERT, NET	+++/++++	(LD)	(LD)
Clozapine	+	+	+	++	+++	+		+	+	++	+++	++	++	++	+++	++	+++	++	++	++		+++/++++	++	++
Chlorpromazine	++	+++	+++	+++	+++	+	+			+++	+++	++	+++	+++	++	++	+++	+	++	++		+++/++++	+/++	+/++
Sertindole		+++	+++	+++	+			+	++	++++		+++		++			+++	+	+	+		+++/++++	+/++	+/++
Iloperidone	+	+++	+++	++	+			++	++	+++		++	+	+			+++	+	+	++		+++/++++	+/++	+/++
Risperidone	+	+++	+++	+++	+++	+		+	++	++++	++	++		+++			+++	++	++	+++		+++	+/++	+/++
(Nor)quetiapine	+	+	+		+++			++		++		+	+	++	+	+	++	+	+	++	NET	+++	+/++	++
Paliperidone	+	+++	+++	+++	++	+		+	++	+++		++	+	+++			+++	+++	+++	+++		+++	+/++	+/++
Asenapine	+++	+++	++++	+++	+++	+++		+++	+++	++++	++++	++++	++++	++++			+++	+++	++++	+++		++	+	+
Amisulpride		+++	+++	+++							++			++								++	+	++(LD)
Aripiprazole		+++	+++	+	++			+++	+	++	++++	++	+	++			++	++	++	++	SERT	++	+	+
Brexpiprazole	+	++++	+++	+++	++			++++	++	++++	+++	+	++	+++			+++	++	++	++++	SERT, NET	+(LD)	+(LD)	+(LD)
Cariprazine		++++	++++		++			+++		++	++++	+		+			+					+(LD)	+(LD)	+(LD)
Haloperidol	+	+++	+++	+++		+			+	+				+			++	+	+	+		+	+	+
Lurasidone	+	+++						+++		+++		+		++++			++	++		+++		+	+	+
Ziprasidone	+	+++	+++	++	++			+++	+++	++++	++	++++	++	+++			++	+	++	++	SERT, NET	+	+	+

S. Siafis, Current Neuropharmacology, 2018, Vol. 16, No. 8

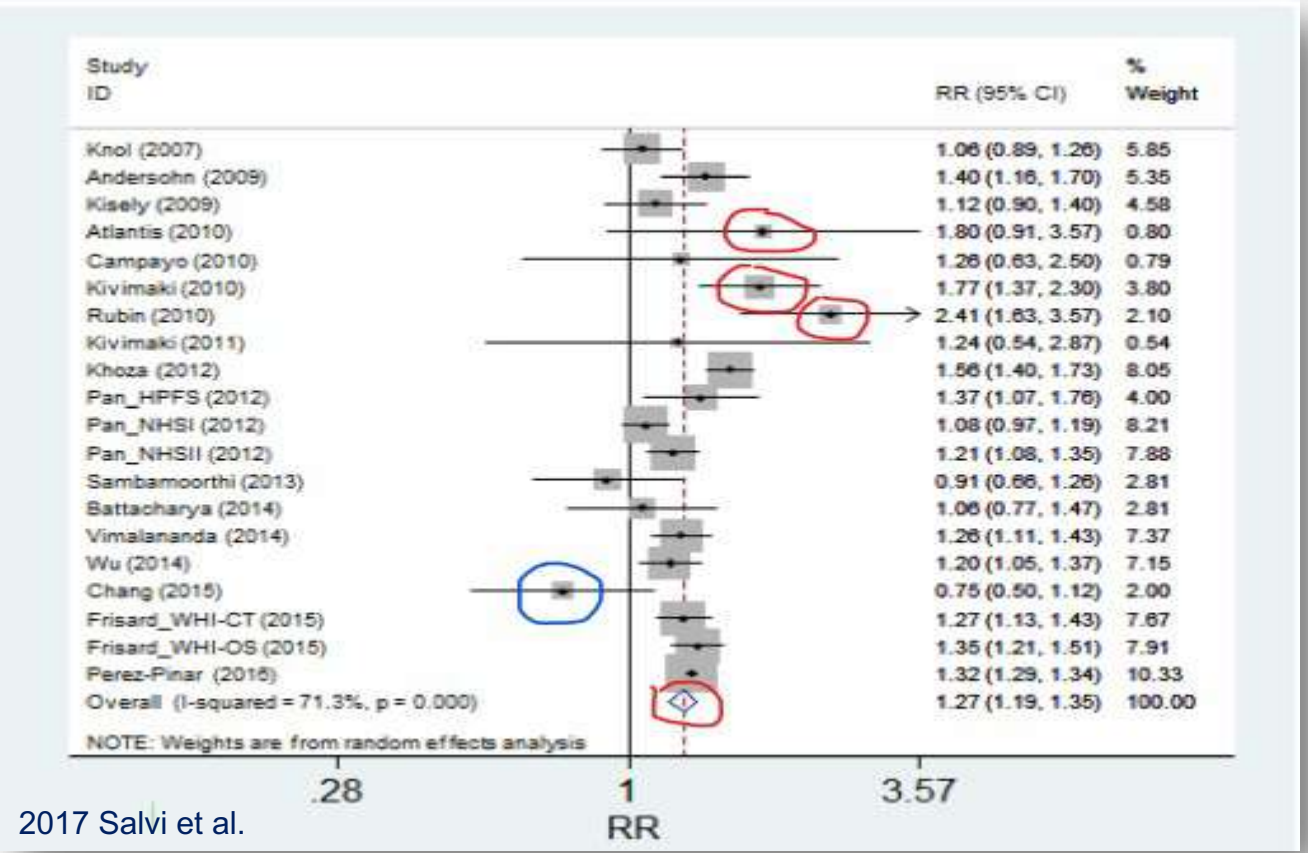
Increased risk of type 2 diabetes in antidepressant users: evidence from a 6-year longitudinal study in the E3N cohort

Methods Data were obtained from the E3N study (*Étude Épidémiologique de Femmes de la Mutuelle Générale de l'Éducation Nationale*), a French cohort study initiated in 1990, with questionnaire-based follow-up every 2 or 3 years. Exposure to antidepressants was obtained from drug reimbursement files

Results Of the 63 999 women who were free of drug-treated type 2 diabetes at baseline in 2005, 1124 developed type 2 diabetes over the 6-year follow-up. Current use of antidepressants was associated with an increased risk of type 2 diabetes [hazard ratio 1.34 (95% CI 1.12, 1.61)] compared to non-users. When the different types of antidepressants were considered, women who currently used selective serotonin reuptake inhibitors, imipramine-type, 'other' or 'mixed' antidepressants had a 1.25-fold (95% CI 0.99, 1.57), 1.66-fold (95% CI 1.12, 2.46), 1.35-fold (95% CI 1.00, 1.84) and 1.82-fold (95% CI 0.85, 3.86) increase in risk of type 2 diabetes compared to non-users, respectively.

M Azevedo Da Silva, Diabet Med. 2020 Nov;37(11):1866-1873

Random effects meta-analysis of the association between use of **ADs and Incidence of Diabetes**.

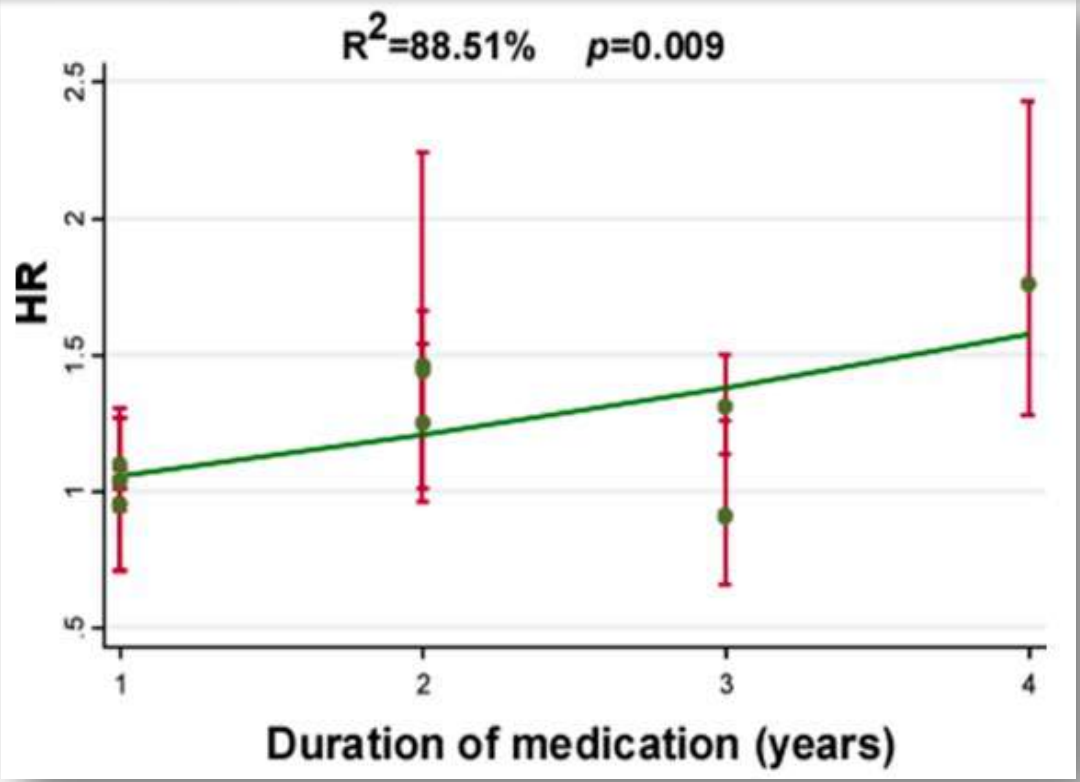


2017 Salvi et al.

Is the link between ADs and diabetes due to ascertainment **bias**?

May **different ADs** carry different risks of type 2 diabetes?

Meta regression analysis of pooled estimates of T2DM and **Duration of Medication** in Antidepressant Users.



Yuqing Wang, 2021

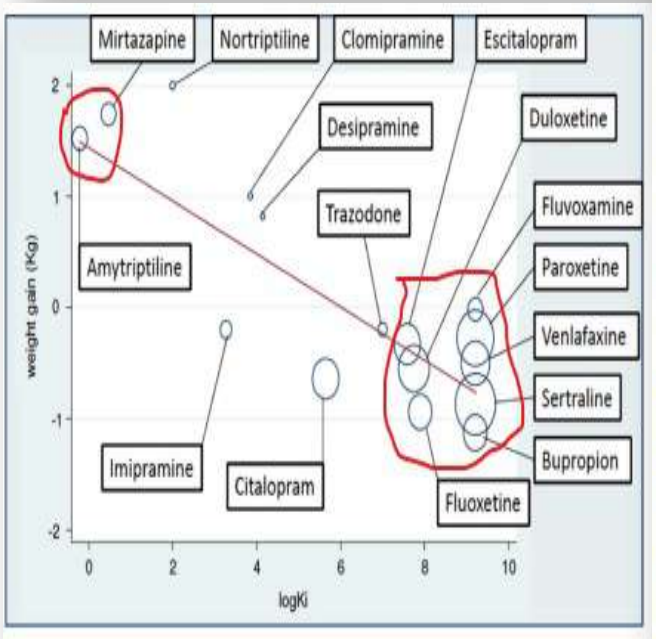
Antidepressants use was a risk factor for the new onset of T2DM, even after depression and BMI were adjusted. TCAs rather than other categories of antidepressants increased T2DM risk. Moreover, there was an increasing linear trend between duration of antidepressants medication and T2DM risk.

It was controversial about whether the antidepressants use could increase the risk of T2DM. As one of the first generation antidepressants, TCAs not only inhibit reuptake of norepinephrine and serotonin but also block postsynaptic histamine, alpha-adrenergic, and muscarinic-acetylcholine receptors causing a variety of adverse effects (Obata, 2017; Schneider et al., 2019), such as orthostatic hypotension, arrhythmias, corrected QT interval changes (Wernicke, et al., 2007) and even metabolic syndrome (Van Reedt Dortland et al., 2010, 2009). The current study indicated that TCAs but not other antidepressants were the potential risk factors for the onset of T2DM. However, there were no significant associations between SSRIs, SNRIs or NaSSAs use and the new onset of T2DM. However, the overall pooled estimates (SSRIs, SNRIs, NASSA and TCAs) was still significant. This could be explained by the fact of combination medication, especially TCAs, which was related to the new onset of T2DM. Due to the limited involved studies, the results might be unstable and biased. Therefore, a large number of prospective studies are needed to confirm the conclusion.

The comorbidity of depression and T2DM should be considered

H1-histamine receptor affinity predicts weight gain with antidepressants

Virginio Salvi[a,*], Claudio Mencacci[a], Francesco Barone-Ades



Abstract

Weight gain and metabolic abnormalities are extensively found in patients taking psychotropic medications. Although mainly antipsychotics have been implicated, also antidepressants carry the potential to induce weight gain, with tricyclics and mirtazapine being associated with the greatest weight gain. It has been suggested that this could be due to the different ability of antidepressants to block adrenergic, cholinergic, and histaminergic postsynaptic receptors. To date, however, the link between antidepressant-induced weight gain and their receptor affinity profile has not been established. We reanalysed data from a previous meta-analysis to evaluate whether weight change is associated with specific receptor affinity of antidepressants.

We retrieved data from the only meta-analysis that assessed weight change with antidepressants. We searched in the Psychoactive Drug Screening Program (PDSP) Ki database data on the affinities of antidepressants to receptors hypothetically linked with weight change: H1-histamine, 5HT2c, M3-muscarinic, and α1A-adrenergic receptors. The association between weight change and receptor affinities was estimated using meta-regression.

We found a significant association between the affinity of antidepressants to H1-receptor and weight gain (p value: <0.001). An association between weight gain and receptor affinity was also observed in the models for 5HT2c, M3, and α1A receptors. However, the association disappeared when H1-receptor was included in the models.

This reanalysis of data demonstrates that anti-histaminergic activity is the strongest predictor of weight gain with antidepressants. These results further stress a reclassification of antidepressants according to their pharmacodynamic properties, and suggest avoiding prescribing antidepressants with an anti-histaminergic profile to patients at risk for cardiometabolic disturbances.

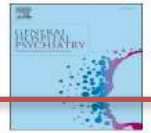
Pharmacological Strategies to Counteract Psychotropic Drugs-Induced Weight Gain and Metabolic Adverse Effects

General Hospital Psychiatry 78 (2022) 58–67

Contents lists available at ScienceDirect

General Hospital Psychiatry

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



Review article

A systematic review of licensed weight-loss medications in treating antipsychotic-induced weight gain and obesity in schizophrenia and psychosis

Kenn Lee [a,*], Seri Abraham [a,b,c], Robert Cleaver [a]

databases for human studies using licensed WLMs to treat AIWG and OSP.

Results: Three RCTs (two liraglutide, one naltrexone-bupropion), one unpublished open-label trial (naltrexone-bupropion), and seven observational studies (five liraglutide, one semaglutide, one multiple WLMs) were identified. Results for liraglutide showed statistically significant improvement in weight, BMI, waist circumference, HbA1c, cholesterol, and LDL readings on meta-analysis. Evidence was mixed for naltrexone-bupropion with no detailed studies conducted for setmelanotide, or stimulants.

Conclusion: Evidence is strongest for liraglutide compared to other licensed WLMs. The findings, particularly the inclusion of human trial data, provide evidence for liraglutide use in treating AIWG and OSP, which would better align psychiatric practice with non-psychiatric practices around obesity. The findings also identify continued literature gaps regarding other licensed WLMs.

Conclusion 1

- **Antipsychotics** and **Antidepressant use** play an essential part of the management of people with severe mental illness; however, this comes at the cost of an **increased risk of weight gain** and **diabetes**

- **Antipsychotics**, especially SGAs, are associated with weight gain and glucose dysregulation, two major contributors to T2D development

- SGAs, in particular olanzapine and clozapine, but also the FGA *chlorpromazine*, can impair Insulin Signaling in Insulin-Sensitive Tissues

- SGAs have a direct effect on β-cell function and insulin secretion probably also on α-cells and associated glucagon secretion

Conclusion 2

- **Long-term Antidepressant use** increased the risk of type 2 diabetes onset in a **time and dose-dependent manner**. Glucose tolerance improved when antidepressants were **discontinued** or the **dose was reduced** after diabetes onset. However, the undellying mechanism is still unclear

- Long term antidepressants use should be evaluated more cautiously for its benefits and the potential risk of Type 2 DM

Conclusion 3

- the first choice of therapy should be an antipsychotic (AP) or antidepressant **with low risk** of metabolic disturbances
- Along with lifestyle intervention, **Metformin** should also be implemented as **first-line therapy** for DM
- As second-line therapy, a **GLP-1RA** (especially liraglu□tide or once-weekly exenatide) or an **SGLT2** inhibitor should be chosen for the management of DM, as they confer additional advantages (weight control, cardiore□nal protection, low risk of hypoglycemia)

Decreased Risk of Anxiety in Diabetic Patients Receiving Glucagon-like Peptide-1 Receptor Agonist: A Nationwide, Population-Based Cohort Study

Wen-Hsuan Tsai[1†], Fung-Chang Sung[2,3,4†], Lu-Ting Chiu[2], Ying-Hsiu Shih[2], Ming-Chieh Tsai[1] and Shu-I Wu[5,6]*

Factors that may contribute to diabetes and other physical health risks in people with severe mental illness.

CONGRESSO REGIONALE
AMD-SID LAZIO

Weight gain effects on medication (antipsychotics and antidepressants)

- **Obesity**, Smoking
- **Poor Diet**, **Physical Inactivity**
- Symptoms of Psychosis (delusions and hallucinations may limit activities)
- Reduced Motivation (illness and medication)
- *Lower Socioeconomic Status*
- *Social Exclusion and Isolation*, *Family Environment*
- Cognitive Deficits and Educational Limitations
- *Sleep Alterations*

V. Mamakou, PsychiatrikI 29 (1), 2018

Elizabeth Blanchard, Diabetes Management (2014) 4(4), 339–353