Mechanisms underlying the metabolic and hormonal side effects of antipsychotic drug treatment

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Current antipsychotic drugs

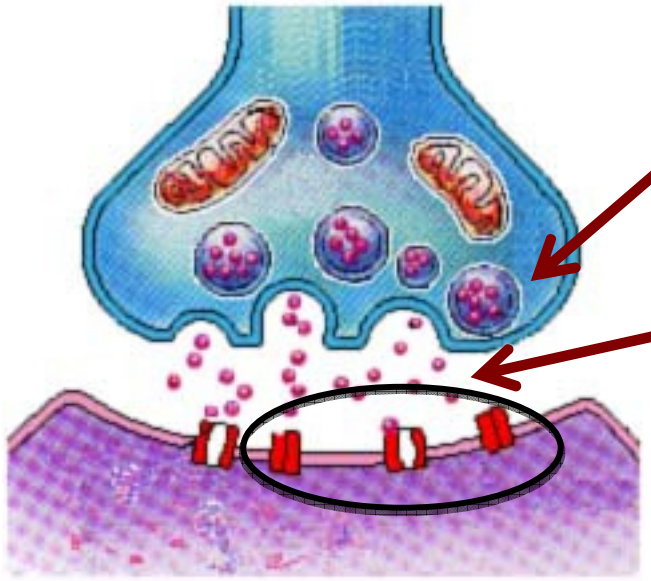
- Classical (typical) antipsychotics
  - Dopamine D2 antagonists
  - e.g. haloperidol, chlorpromazine, flupentixol
- Second generation (atypical) antipsychotic drugs
  - Dopamine D2 and serotonin 5-HT2 antagonists
  - e.g. risperidone, olanzapine, quetiapine, asenapine
- Partial dopamine agonist - aripiprazole
  - with additional 5-HT receptor effects
- Clozapine
  - The only antipsychotic approved for treatment resistant patients

Antipsychotic drug treatment

- The efficacy of antipsychotic drug treatment can vary, both between drugs (a little) and between patients (a lot).
- The limiting side effects of antipsychotic drugs also vary between drugs and between patients, e.g:
  - extrapyramidal symptoms
  - metabolic changes
  - hormonal changes
- Receptor pharmacology helps us to understand the action of antipsychotic drugs on disease symptoms and side effects.

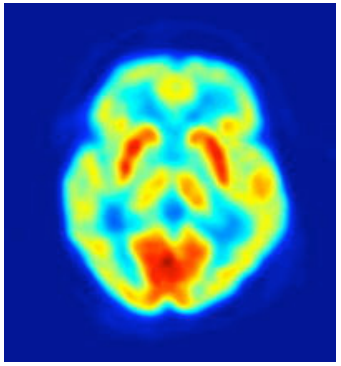
Dopamine in schizophrenia

Dopamine is important in understanding the positive symptoms of schizophrenia and the effect of antipsychotic drugs:



Dopamine storage ↑

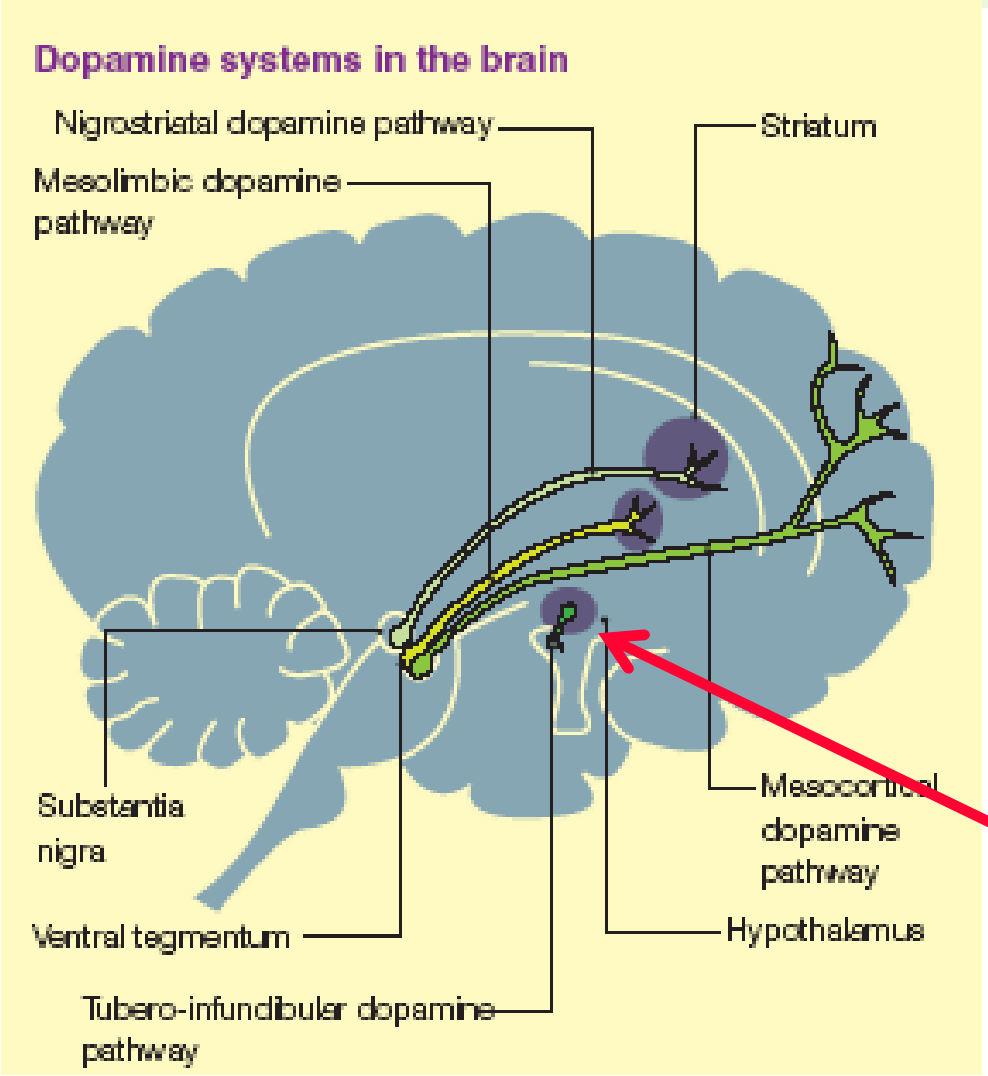
Dopamine release ↑



Antipsychotic drugs block dopamine D2 receptors

But dopamine hyperfunction is not the *primary* pathology of schizophrenia.

Dopamine pathways in the brain



Mesolimbic pathway

Blockade of limbic dopamine receptors may alleviate positive psychotic symptoms

Nigrostriatal pathway

Involved in motor control; blockade of striatal D2 receptors causes EPS

Mesocortical pathway

Dopamine in frontal cortex mediates cognitive functions

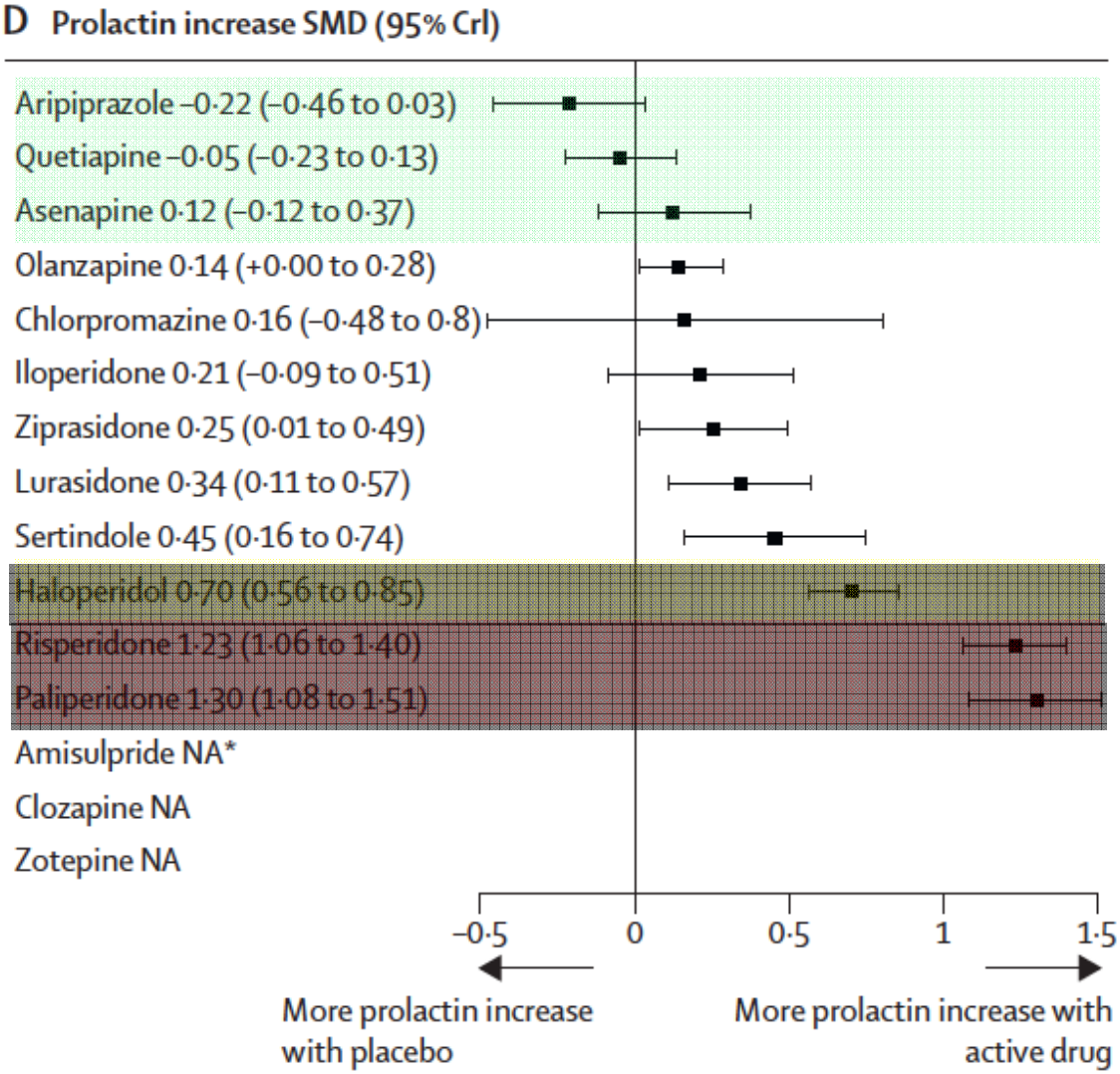
Tuberoinfundibular pathway

Controls secretion of prolactin i.a.

Control of prolactin secretion

- Dopamine provides inhibitory control of prolactin secretion into the blood from the pituitary gland
- Other factors influence prolactin secretion:
  - Physiological: stress, sexual activity, pregnancy etc…
  - Pathological: pituitary tumour, hypothalamic disease etc...
- Prolactin can suppress sex hormones with effects including:
  - Sexual dysfunction
  - Osteoporosis

Meta-analysis of antipsychotic drug-induced prolactin secretion



- Risperidone and paliperidone induce more prolactin secretion than all other antipsychotics.
- Haloperidol has a lesser effect but is significantly greater than most other antipsychotics.
- Aripiprazole, quetiapine and asenapine have effects on prolactin not significantly different from placebo.

From Leucht et al, 2013

Control of prolactin secretion – antipsychotics 1

- Antipsychotic drugs block dopamine D2 receptors, causing disinhibition of prolactin release
- Drugs with high D2 antagonist affinity, and/or with poor brain penetrance, have greatest effects on prolactin
  - haloperidol, risperidone, amisulpride

Brain-blood ratios of some newer antipsychotic drugs

	Brain-blood ratio
Clozapine	*24*
Olanzapine	*≈10*
Quetiapine	*≈10*
Risperidone	*0.22*
Paliperidone	*0.04*

Rat brain data from
Aravagiri et al (1998;1999)

Relatively lower brain levels of risperidone and paliperidone are maintained by activity of the p-glycoprotein pump.

Dopamine D2 receptors in the pituitary are not protected by an effective blood-brain barrier.

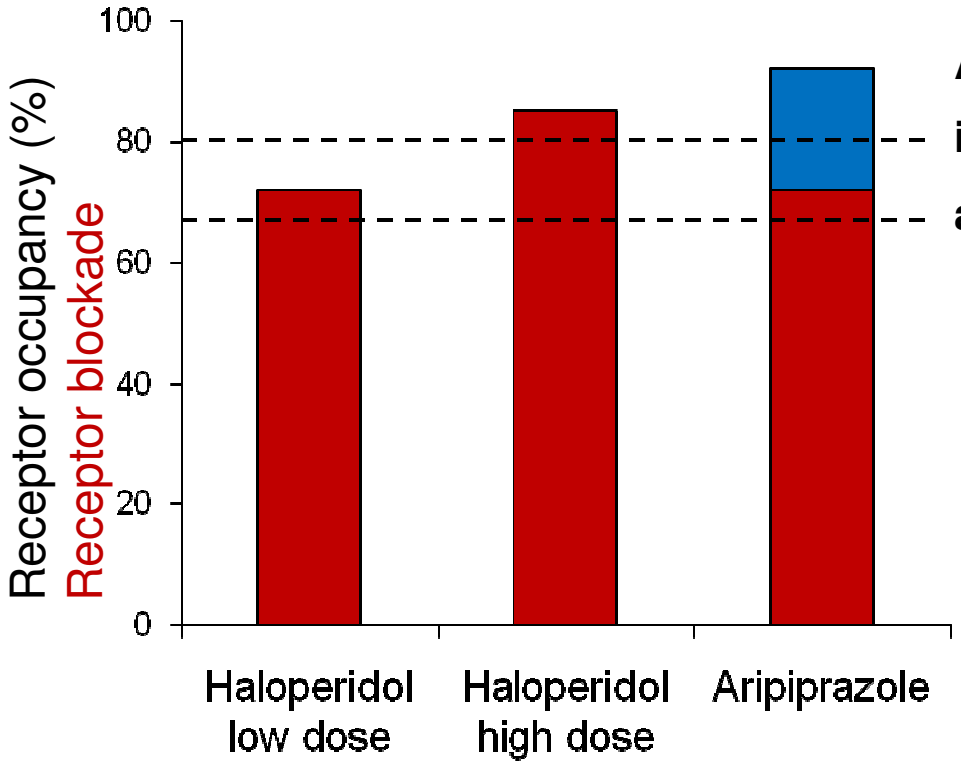
The higher blood levels for risperidone and paliperidone result in relatively greater antagonism of pituitary vs. striatal/limbic D2 receptors.

Control of prolactin secretion – antipsychotics 2

- Antipsychotic drugs block dopamine D2 receptors, causing disinhibition of prolactin release
- Hyperprolactinaemia may be avoided/diminished by:
  - partial agonism at the D2 receptor (aripiprazole)
  - Weak affinity for the D2 receptor (clozapine, quetiapine)
  - antagonism at the 5-HT2C receptor (olanzapine, clozapine, asenapine)

Reynolds GP (2004) J Psychopharmacol 18, 340-345

D2 partial agonism of aripiprazole and the threshold for EPS



Haloperidol is a full antagonist and will block agonist effects of dopamine at the D2 receptor.

Aripiprazole is a partial agonist and will partially stimulate and partially block the receptor.

Sexual dysfunction and hyperprolactinaemia

Sexual dysfunction is common in serious mental illness and is under-reported and under-investigated.

There are multiple aetiological factors including:

- Drug-related factors:
  - Hyperprolactinaemia from D2 receptor antagonism
  - Alpha1 adrenoceptor antagonism
  - Muscarinic receptor antagonism
- Disease- or life style-related factors:
  - Vascular pathology (secondary to e.g. smoking)
  - Drug misuse, inadequate diet

Association of antipsychotic treatment with sexual dysfunction in men

100 married Chinese men with schizophrenia in remission had sexual dysfunction assessed by ASEX score (>19 threshold) and erectile dysfunction by IIEF score (<21 threshold). *Zhang et al (2011)*

Treatment	No. of subjects	Age (y)	Prolactin	ASEX score	Sexual (erectile) dysfunction
Typical antipsychotics	30	41.9 ± 3.7	17.8 ± 13.0	20.7 ± 5.6	n=20 (18) 67% (60%)
Clozapine	37	42.0 ± 3.0	12.1 ± 10.2	17.2 ± 6.0	n=15 (14) 41% (38%)
Risperidone	30	38.3 ± 6.7	31.9 ± 22.3	17.0 ± 5.2	n=12 (13) 40% (43%)
P		*n.s.*	*<0.001*	*<0.02*	*0.06 (0.18)*
P(typical vs atypical)					*0.01 (0.05)*

Data expressed as mean ± s.d.

Sexual dysfunction was not associated with increased age or duration of treatment.

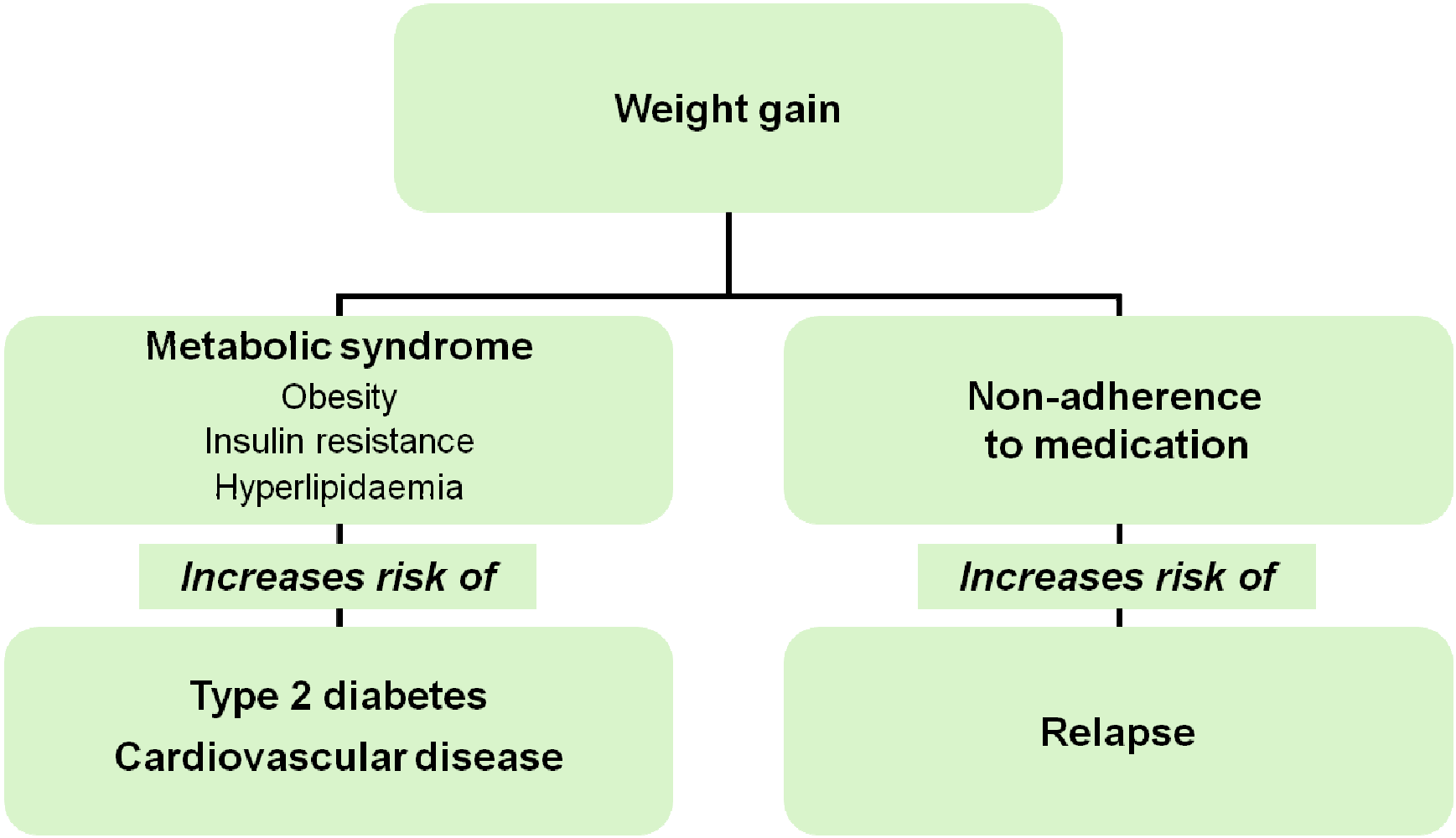
Association of antipsychotic treatment with sexual dysfunction in men

- Sexual dysfunction is not closely related to prolactin concentrations
  - Patients receiving risperidone had higher prolactin than those on typical antipsychotics
  - Sexual and erectile dysfunction was greatest in those receiving typical antipsychotics
- Other factors in addition to prolactin contribute to antipsychotic-induced male sexual dysfunction, e.g:
  - Alpha1 adrenoceptor antagonism
  - Muscarinic receptor antagonism

Proposed pharmacological mechanisms underlying effects of antipsychotic drugs

Effect:	**Antagonist action at:**
Antipsychotic/anti-manic	***Dopamine D2 receptors in limbic brain***
Extrapyramidal side effects (parkinsonism etc)	***Dopamine D2 receptors in basal ganglia***
Hyperprolactinaemia (leading to amenorrhoea etc)	***Dopamine D2 receptors in pituitary***
Enhanced response of depressive/negative symptoms	***5-HT1A receptors, 5-HT2 receptors etc.***
Reduced extrapyramidal side effects	***Muscarinic acetylcholine receptors, 5-HT2 receptors in basal ganglia etc.***
Weight gain and other metabolic effects	***5-HT2C receptors in hypothalamus; perhaps histamine H1, muscarinic M3 and D2 receptors***
Sedation	***Histamine H1 receptors***
Postural hypotension	***Alpha1 adrenoceptors***

Consequences of antipsychotic-induced weight gain



Mortality in schizophrenia

A population-based study of mortality in schizophrenia (FIN11) showed:

- Life expectancy at age 20y is lower than the general population by 22.5y.
- Antipsychotic drug use does not additionally increase mortality in patients with schizophrenia.
- Among antipsychotics, quetiapine and risperidone had the highest mortality risk, clozapine the lowest.
- There was no relative elevation in cardiovascular mortality in patients receiving olanzapine or clozapine.

(Tiihonen et al, 2009)

Metabolic pathology in schizophrenia – disease-related factors

There may be disease-associated factors that increase risk.

Some examples:

- Poor self-care, resulting in poor diet with over-reliance on high carbohydrate foods, could lead to overweight.
- High stress as a response to psychotic symptoms, particularly in poorly responding or inadequately treated patients, can result in metabolic disturbances.
- Smoking may increase risk for metabolic disturbances.

Metabolic pathology in schizophrenia

- There is conflicting evidence whether young, untreated patients with schizophrenia have any metabolic abnormality.
- Studies of drug-naïve subjects show:
  - No increase in glucose, insulin or other metabolic indicators (n=121), or in fat deposits by MRI (n=40) – *Zhang et al (2004)*
  - No increase in fasting glucose, insulin or BMI (n=50) – *Arranz et al (2004)*
  - Increase in intra-abdominal fat (n=19) – *Ryan et al (2004)*
- But there is consistent observation of increased incidence of diabetes in first-degree relatives of schizophrenics.

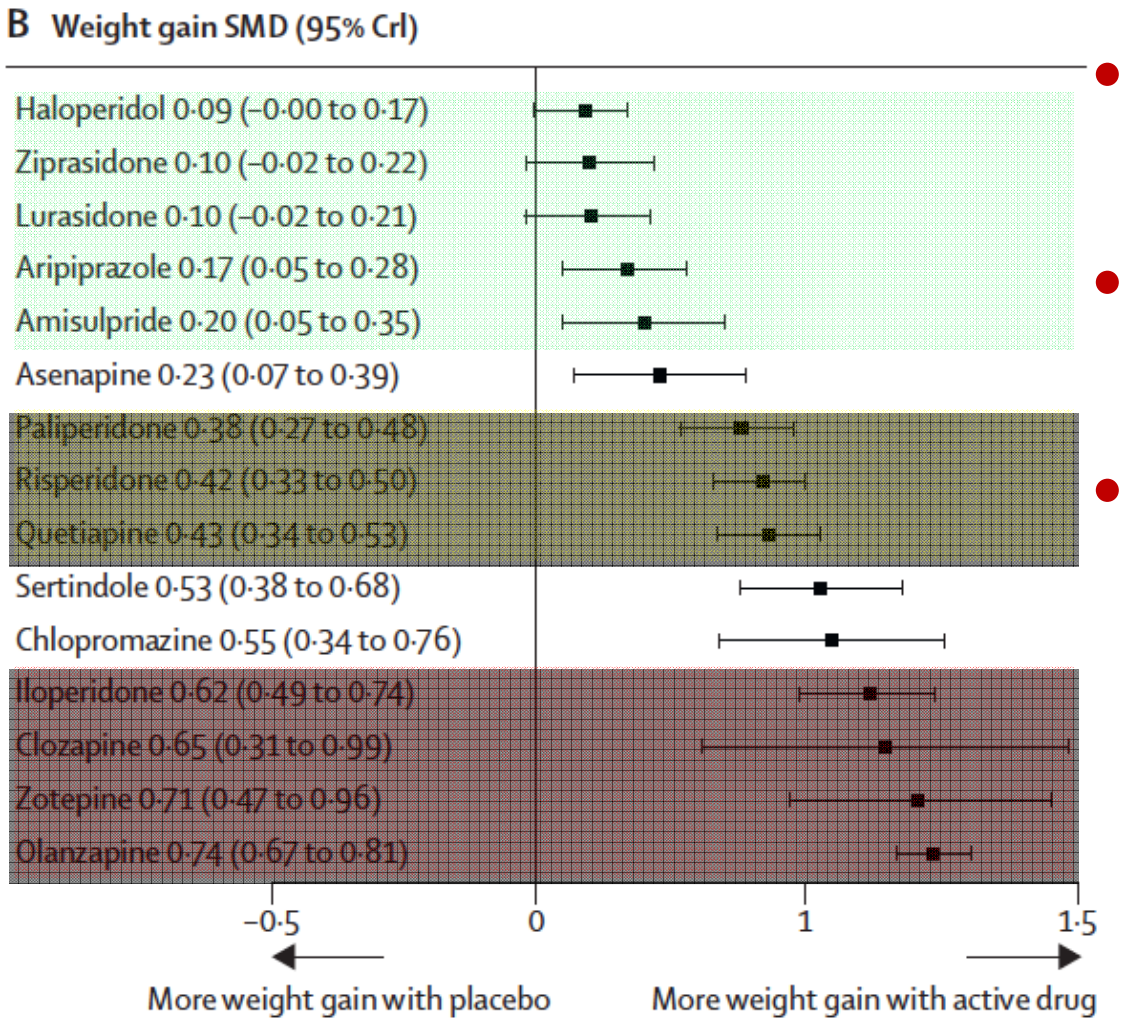
Metabolic disturbances in chronic schizophrenia

A study of metabolic disturbances in schizophrenia in the Northern Ireland population (n=134):

- Patients assessed for BMI, central obesity, random blood glucose, triglycerides, cholesterol and blood pressure i.a.
- Obesity:
  - 99/133 (74%) had central obesity defined by waist circumference (≥ 94cm males; ≥ 80cm females)
  - 55/133 (41%) had obesity defined by BMI>30
- Metabolic syndrome defined by IDF criteria:
  - present in 46/120 (38%) (c.f. 36% in *De Hert MA et al.2006 Schiz Res 83: 87-93).*

(Yevtushenko et al (2008) Brit J Psychiat 192, 424-8)

Meta-analysis of antipsychotic drug-induced weight gain



- Olanzapine has greater weight gain than all other antipsychotics (except zotepine).
- Only haloperidol, lurasidone and ziprasidone do not differ significantly from placebo.
- Apart from the wide range of relative weight gain reported for clozapine, three non-overlapping groups of antipsychotic drugs can be distinguished.

From Leucht et al, 2013

Weight gain following antipsychotic treatment in first episode, drug-naïve patients

In 41 Chinese patients receiving risperidone or chlorpromazine:

- At 10 weeks BMI increased by 7.7%
  (reflecting an increase in fat mass determined by MRI)

(Zhang ZJ et al (2004) Brit J Psych 184, 58-62)

In 87 Spanish patients receiving mainly risperidone or olanzapine:

- At 3 months BMI increased by 10.1%.
  - 7.4% risperidone, 13.1% olanzapine
- At 9 months BMI increased by 17.1%.
  - 13.7% risperidone, 21.1% olanzapine

(Templeman et al, 2005 Pharmacogenetics 15, 195-200)

Fat and glucose metabolism in schizophrenia - effect of initial antipsychotic treatment

	Glucose post-fast	Trigly-cerides	Chol-esterol	LDL	Leptin
Before treatment	6.34 ±1.61	1.15 ±0.60	4.08 ±0.83	2.19 ±0.96	7.68 ±7.71
After 10 weeks' treatment	7.18** ±1.65	1.66*** ±0.67	4.58*** ±0.95	2.63** ±0.85	21.61*** ±17.13

**p<0.01, ***p<0.001

There were no significant changes in fasting insulin or glucose.

(Zhang ZJ et al (2004) Brit J Psych 184, 58-62)

Consequences of antipsychotic treatment of drug-naïve patients

- Rapid weight gain with substantial deposition of both subcutaneous and intra-abdominal fat.
- Elevations of glucose and lipid markers, with potential cardiovascular and diabetic consequences.
- Elevation of leptin secretion.

(Zhang ZJ et al (2004) Brit J Psych 184, 58-62)

Leptin

Leptin is a circulating hormone released by adipose tissue to have effects on the brain in controlling food intake.

Deficits in leptin and leptin receptors result in obesity.

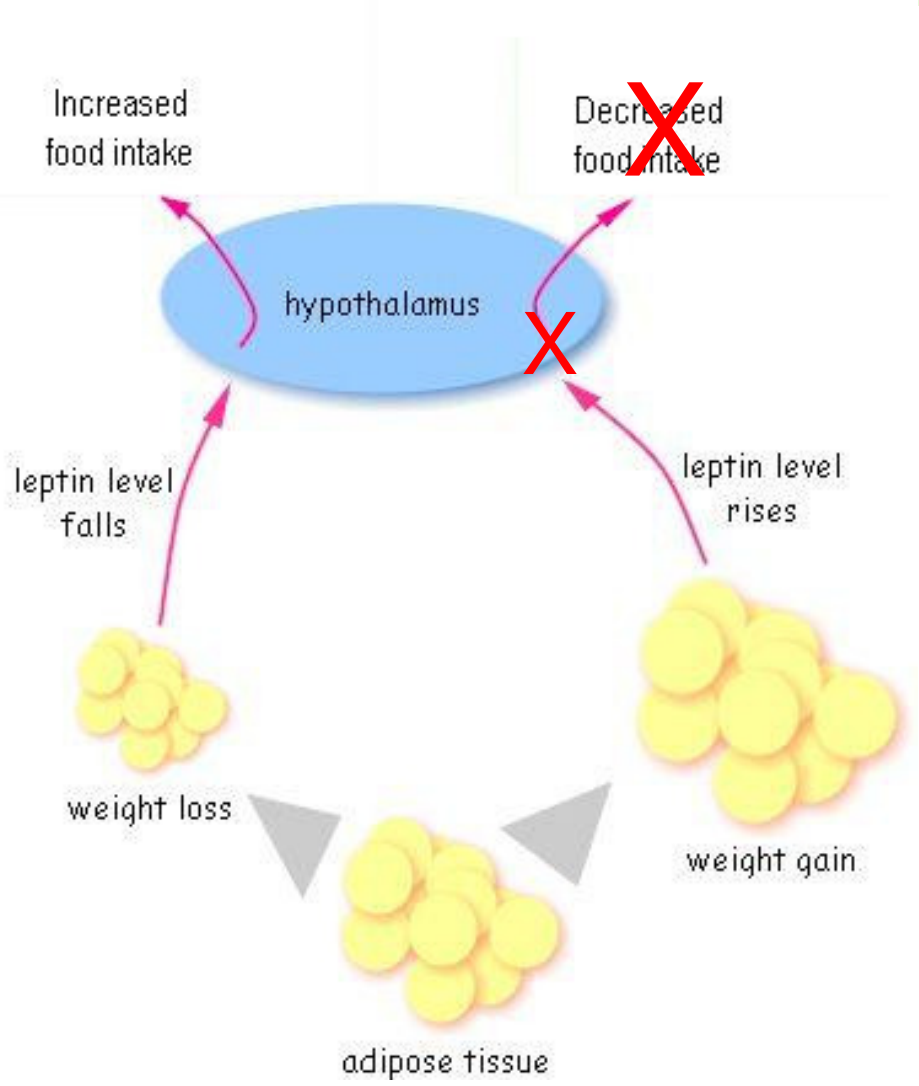
Mouse on right lacks leptin receptors

Leptin, fat and food intake

As fat is deposited, the secretion of leptin increases, to signal to the brain to decrease food intake.

Patients receiving antipsychotic drugs have increases in leptin in parallel with their increase in weight. But they still have increased appetite.

This suggests that treatment with some antipsychotic drugs, perhaps via blockade of 5-HT2C and other receptors, results in the loss of the normal control of food intake provided by leptin.



Antipsychotic-induced weight gain – receptor mechanisms

Mechanisms contributing to antipsychotic drug-induced weight gain might include antagonism at:

- Serotonin 5-HT2C receptors
- Histamine H1 receptors
- Muscarinic M3 receptors
- Dopamine D2 receptors
- etc...

Clozapine and olanzapine have effects at all these receptors.

Olanzapine-induced weight gain can be modelled by a combination of 5-HT2C (but not H1) antagonism and D2 antagonism in the rat

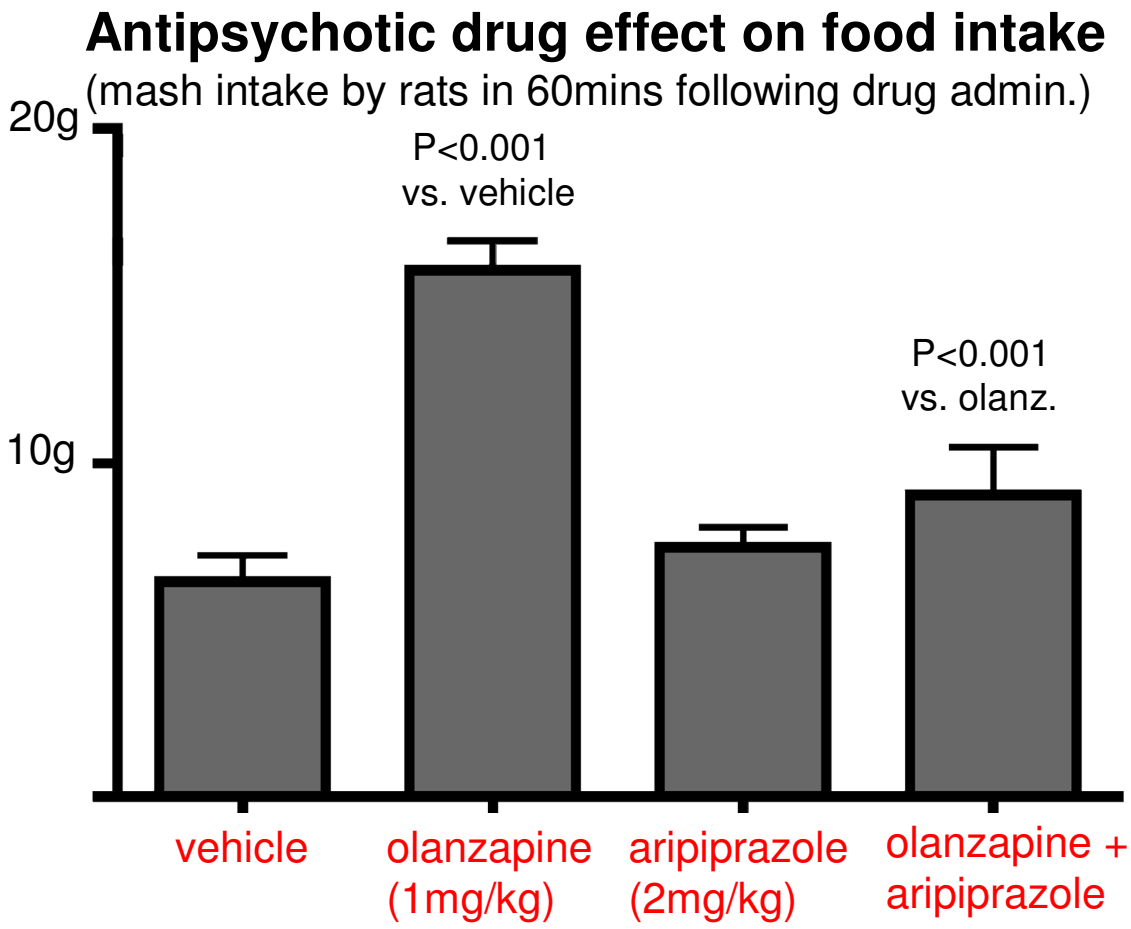
(Kirk et al 2009 Psychopharmacology 207, 119-125)

Mechanisms influencing antipsychotic weight gain

Other mechanisms may determine why some drugs do not show the weight gain associated with clozapine and olanzapine

- There may be protective pharmacological mechanisms:
  - For example, aripiprazole and ziprasidone can protect against the effects of olanzapine on hyperphagia in animals (*Kirk et al, 2004; Snigdha et al 2008*).

Aripiprazole protects against the effect of olanzapine on food intake



(Snigdha et al (2008) J Psychopharm 22, 567-571).

- Aripiprazole suppresses the acute effect of olanzapine on food intake in rats.
- The relative freedom from weight gain with aripiprazole may relate to a protective mechanism.
- This effect has also been seen with ziprasidone *(Kirk et al, 2004)*.

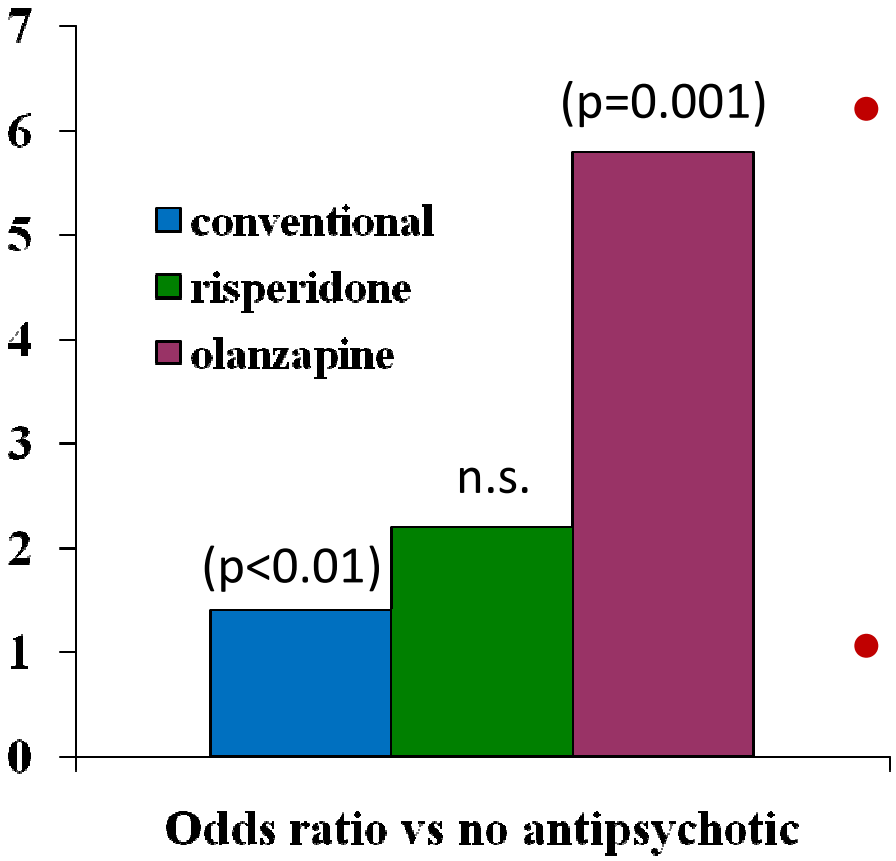
5-HT receptors and protection from weight gain

- The relatively limited weight gain associated with aripiprazole may relate to a protective mechanism, rather than simply the lack of a hyperphagic effect.
- This protective effect has been observed in the clinic, in conjunction with olanzapine *(Chen et al, 2007)* and with clozapine *(Masopust et al, 2008)*.
- The possible mechanisms that might contribute to this protective effect against weight gain include:
  - D2 partial agonism
  - 5HT1A partial agonism
  - 5-HT2C partial agonism

(Reynolds and Kirk (2010) Pharmacol Ther 125, 169-179)

Diabetes following antipsychotic treatment

Diabetes risk in the UK General Practice Research Database of 19637 patients with schizophrenia *(Koro et al 2002)*



- Risk of diabetes (as odds ratio vs. untreated subjects) after:
  - Conventional antipsychotics 1.4
  - Risperidone 2.2
  - Olanzapine 5.8
- Olanzapine is 4.2 times more likely to cause diabetes than conventional antipsychotics.

Diabetes in schizophrenia

Diabetes in schizophrenia is complex, with probably three aetiologies:

- a hereditary relationship independent of drug treatment
  - Diabetes prevalence is increased almost two-fold in unaffected relatives of patients with non-affective psychosis (van Welle et al, 2013)
- an acute, rare, possibly reversible, diabetes following antipsychotic treatment and leading to ketoacidosis
  - Some drugs, notably clozapine and olanzapine, may have a direct effect on glucose regulation independent of adiposity (Newcomer, 2005)
- the long term consequences of drug-induced weight gain and metabolic syndrome.

Muscarinic receptors and antipsychotic drug-induced diabetes

- Drug liability to induce diabetes is reportedly correlated with drug antagonism at muscarinic M3 receptors (*Silvestre and Prous, 2005*).
- M3 receptors control insulin release from pancreatic islet cells; M3 antagonism by clozapine and olanzapine may induce insulin resistance (*Johnson et al, 2005*).
- Clozapine and olanzapine have the highest relative affinities for M3 receptors (*Reynolds and Kirk, 2010*).

Muscarinic M3 receptor affinities of some newer antipsychotic drugs

	D2 affinity	M3 affinity	Relative affinity
Aripiprazole	*0.95*	*>1000*	*$<10^{-2}$*
Asenapine	*1.3*	*>1000*	*$<10^{-2}$*
Clozapine	*431*	*25*	*17*
Lurasidone	*1.7*	*>1000*	*$<10^{-2}$*
Olanzapine	*72*	*51*	*1.4*
Paliperidone	*9.4*	*>1000*	*$<10^{-2}$*
Quetiapine	*567*	*1943*	*0.29*
Risperidone	*4.9*	*>1000*	*$<10^{-2}$*
Ziprasidone	*4.0*	*>1000*	*$<10^{-2}$*

Receptor affinity data are K_D values in nM

Weight gain following antipsychotic treatment in first episode schizophrenia

In 87 Spanish patients receiving mainly risperidone or olanzapine:

- At 3 months BMI increased by 10.1%.
  - 7.4% risperidone, 13.1% olanzapine
- At 9 months BMI increased by 17.1%.
  - 13.7% risperidone, 21.1% olanzapine
- Increase in BMI for olanzapine-treated patients after 9 months varied between 0% and 74% of body weight.

(Templeman et al, 2005 Pharmacogenetics 15, 195-200 and unpublished data)

Antipsychotic drug-induced weight gain

Why do antipsychotic drugs differ in their propensity to induce weight gain? - pharmacology

Why do individuals differ in their liability to drug-induced weight gain? - pharmacogenetics

Metabolic disease and antipsychotic treatment

- Weight gain may be the initial process leading to metabolic and cardiovascular disease – causes of reduced life expectancy in schizophrenia.
- Antipsychotic drugs blocking 5-HT2C and/or other receptors may interfere with the hormonal control of food intake.
- These metabolic consequences of drug treatment are seen with many, but not all, antipsychotics, typical and atypical.
- Several risk factors, other than drug treatment, may influence the emergence of obesity and metabolic syndrome:
  - Modifiable factors: smoking, diet, exercise etc.
  - Unmodifiable factors: genetic variability, age etc.

Antipsychotic drug treatment – present problems, future prospects

Present problems with antipsychotic drug treatment:

- Severe side effects, including
  - weight gain and related metabolic consequences
  - consequences of raised prolactin
- Poor response of negative, depressive and cognitive symptoms

Future prospects in treating psychosis include:

- Better drugs that ameliorate the pathology of schizophrenia
- Genetic testing for individual assessment of
  - severity of side effects
  - likelihood of good symptom response to treatment