بسم الله الرحمن الرحيم

Weight gain caused by medicines

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'All drugs are dangerous, Some may also be useful'

N. Moore, BMJ, 2005, 330;539-40

Every medicine is used to treat a particular condition and has different effects on each patient. Human anatomy is a very complex subject; you can never be sure of the same effects on every patient being treated under same circumstances. The effect of every medicine varies from one patient to another depending upon how the anatomy of a patient reacts to the chemical composition of that particular medicine.

Weight gain side effect of medications

- Many commonly used medications may cause weight gain.
- The amount of weight gained may vary depending on the patient and type of medication.
- In some cases, this happens quickly. But in other cases, it happens more slowly.
- Some medications are more common than others to boost weight, and not all patients will gain weight from every drug that has weight gain listed as a side effect.
- It is often difficult to distinguish between weight gain from a drug and weight gain from other reasons, like diet or lack of exercise, because it can be a slow process. Some conditions, like depression, can lead to weight loss or, more rarely, weight gain, depending upon the person.
- Worries about weight gain or loss should not be the main deciding factor for needed medical treatment.

- The mechanism of weight change effected medicines is poorly understood, and may in large part have an underlying genetic basis.
- A weight gain of >2.0 kg within a month, in the absence of health and lifestyle changes suggests that intervention may be necessary.

The biology of weight

Many biological factors have been implicated in the pathogenesis of obesity:

- An imbalance between energy intake and energy expenditure
- A complex interaction between environmental factors, central nervous system, neurotransmitters (e.g., serotonin, glutamate, GABA, and so on), neurotransmitter receptors, peripheral endocrine systems and some circadian rhythms influence food energy intake and expenditure.
- In the vast majority of cases, the role that an **individual's genetic** makeup plays in the pathogenesis of this imbalance is polygenic.

What can we do to prevent medicine-related weight gain?

A weight gain of >2.0 kg within a month, in the absence of health and lifestyle changes suggests that intervention may be necessary.

- Pay a little more attention to the diet (low carb & sugar)
- Increase in exercise
- Limiting salt intake
- If lifestyle changes alone do not result in the desired amount of weight loss, changes to medication should be considered.
- Where possible, changes to the dose of the medication should be attempted prior to medication substitution.

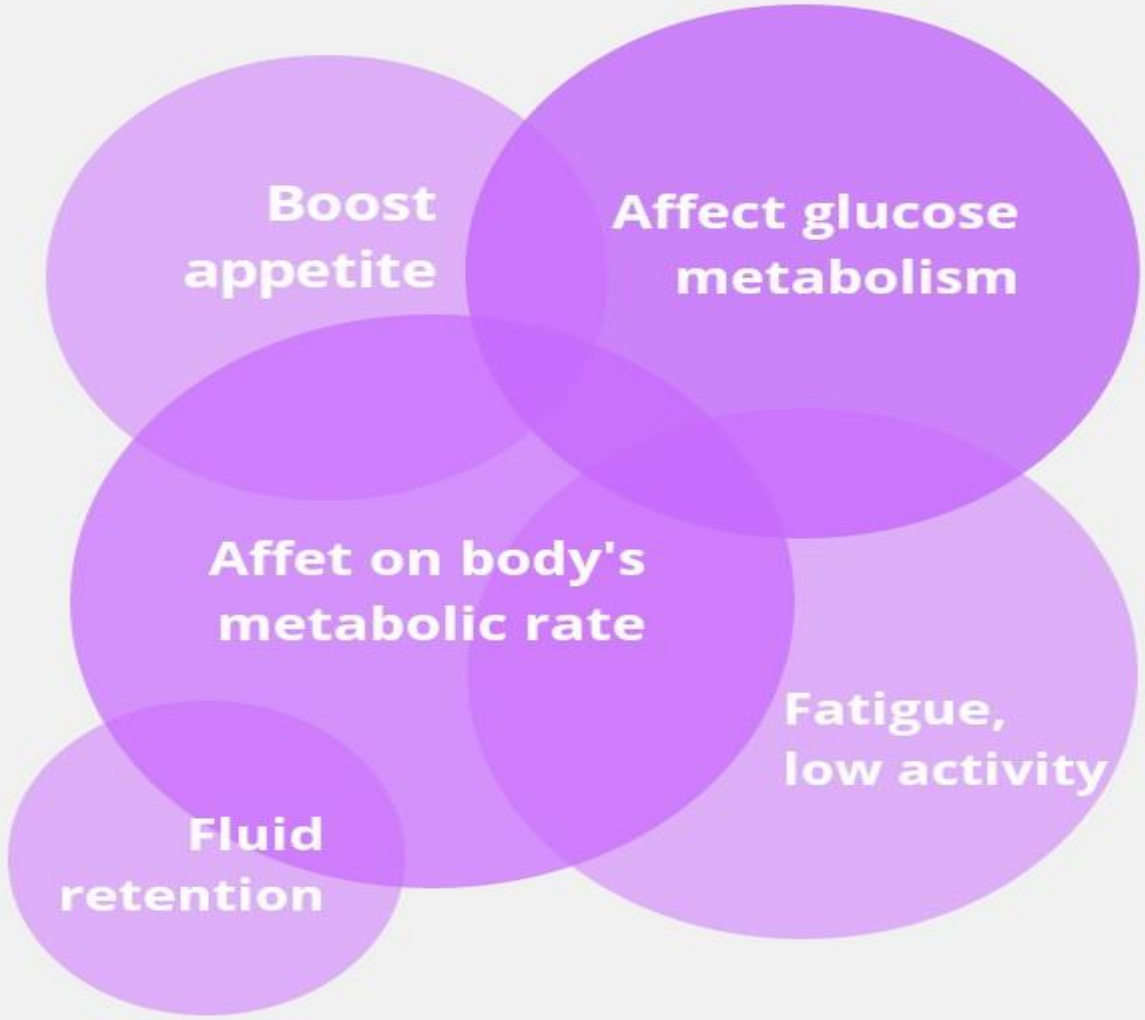
- When switching to a more weight-favorable medication, **non-weight-related side effects** must also be taken into consideration. For example, while bupropion is often recommended as an alternative therapy to other antidepressants due to its weight loss side effects, **it is also associated with a risk of seizures**.
- Further, cost is an important consideration as it can contribute to nonadherence. This may be the case with **liraglutide** 1.8 mg, which is associated with a better side effect and weight profile than other antihyperglycemic medications, but costs considerably more.
- Adjunctive therapies may be used to better manage treatment-induced weight gain (Orlistat, a lipase inhibitor).

What are possible complications?

Being overweight is a risk factor for, or may worsen, many health problems include:

- Diabetes or impaired glucose tolerance
- Arthritis
- High blood pressure
- Heart disease
- Stroke
- Sleep apnea
- Liver disease
- Certain lung diseases
- Infertility
- Certain cancers
- Psychological problems

How do drugs cause weight gain?



How do Medicines Cause Weight Gain?

Medicine-related weight gain can have many causes:

- **Stimulation of appetite**

Some medicines might stimulate patient's appetite. This indirectly effect on receptors in the brain which will stimulate appetite and cause to eat more and gain extra weight (depression medicines)

- **Stimulation of fat storage and glucose metabolism**

Other medicines might affect how the body stores and absorbs sugars and other nutrients. Medicines for diabetes (sulfonylureas class) work by increasing insulin production which lowers blood sugar levels and result in an increased appetite. Injectable insulin also lead to weight gain by allowing glucose to build up in cells instead of staying in the blood. This slowly leads to fat deposit in the body if don't burn it off with exercise.

- **Slowed metabolism**

Some medicines might affect the body's metabolism. This cause body to burn calories at a slower rate.

- **Fluid retention**

Medicines might cause to retain water. This makes body weigh more even if you don't put on extra fat.

- **Impaired exercise tolerance**

If a medicine cause to be tired or have shortness of breath, patient might be less likely to exercise. This can cause slowly lead to weight gain over a period of time due to fatigue and lower activity (blood pressure medicines)

- For certain medicines, researchers aren't exactly sure what triggers the weight gain
- Keep in mind that depression itself can affect patient's appetite and eating habits
- Other causes such as menopause or pregnancy can cause weight gain

Which medicines cause weight gain?

The following classes of medications are associated with weight gain:

- Anti-depressants, anti-anxiety, mood stabilizers:
  - Selective serotonin reuptake inhibitors (SSRIs): Paroxetine, Sertraline, Citalopram, Fluoxetine
  - Older anti-depressants(TCA): Amitriptyline, Imipramine, Nortriptyline, Doxepin
  - Monoamine oxidase inhibitors (MAOIs)
  - Lithium
  - Benzodiazepines
- Anticonvulsants, anti-migraine, neuropathic pain:
  - Gabapentin, Pregabalin, Valproic acid, Carbamazepine, Divalproex

- Antipsychotics:
  - Olanzapine, Clozapine, Risperidone, Quetiapine, Aripiprazole, Haloperidol
- Diabetes medications:
  - Insulin: Both short- and long-acting
  - Sulfonylureas: Glimepiride, Glipizide, Glyburide
  - Thiazolidinedione: Pioglitazone
  - Other: Nateglinide, Repglinide
- Steroid hormones:
  - Synthetic progestins: Medroxyprogesterone, Norethindrone, Levonorgestrel
  - Contraceptives: Oral contraceptive pills
  - Corticosteroids: Prednisone, Methylprednisolone, Prednisolone
  - Chemotherapy: Tamoxifen

- Anti-hypertensive:
  - Beta-blockers: Atenolol, Metoprolol, Propranolol
  - Alpha-blockers: Clonidine
- Antihistamines: Diphenhydramine, Fexofenadine, Cetirizine

- If any of these medications need to be used and no alternative available, it is important to reassure the patient that weight loss and maintenance is still possible despite the effect of the medication.

- It's important to note that not all medicines of these types cause weight gain. For example, the diabetes medicine **metformin** might make you lose weight instead of gain it. **Topiramate** (a medicine used for seizures and migraines) also can help a person lose weight.

CNS disorders medications

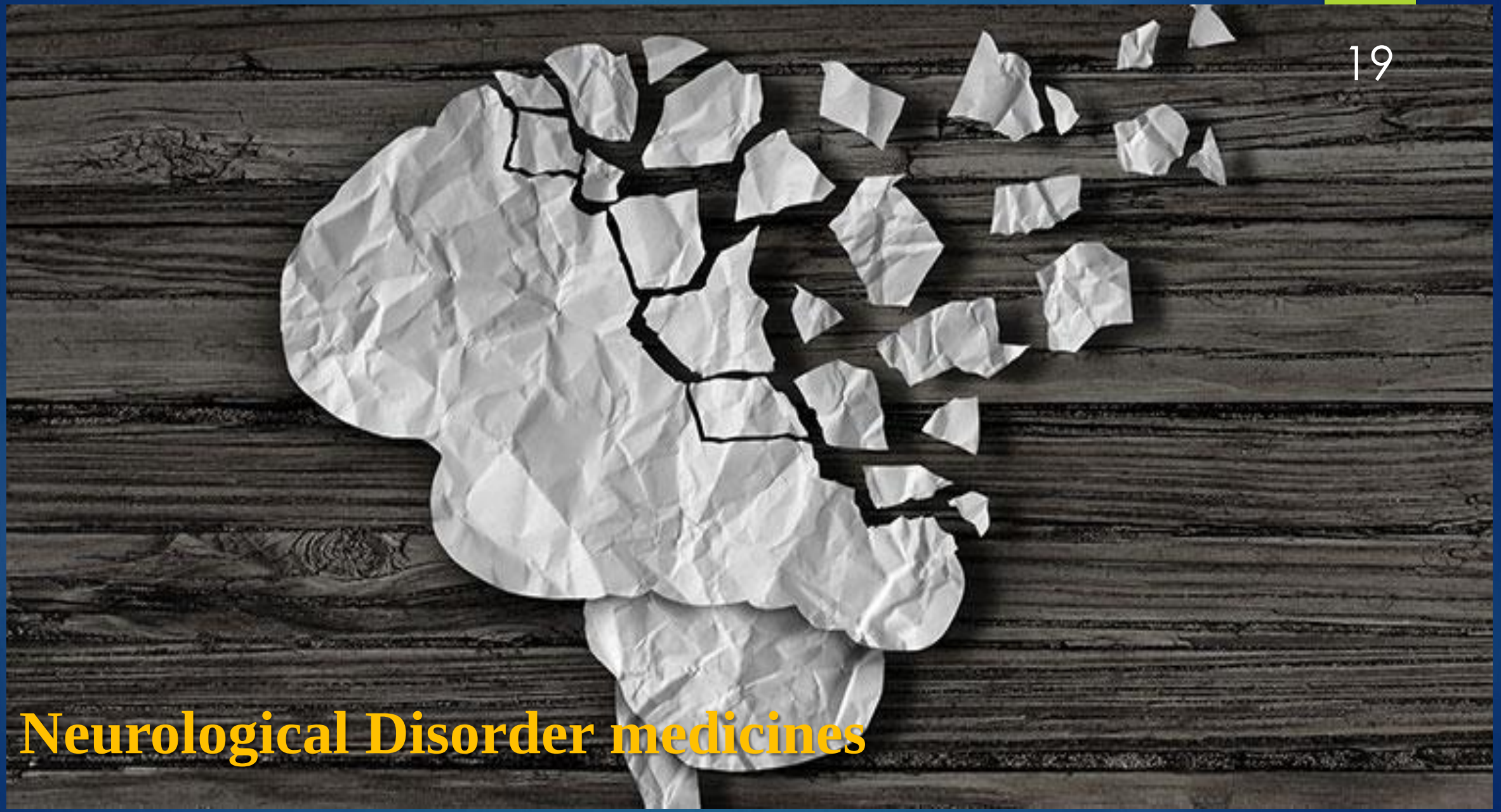
Neuropharmaceuticals

- Most of the neuropharmaceuticals exhibit their effects by targeting either the axonal or synaptic processes of neuron communication or by modifying the signal transduction process.
- The key drug classes used to treat CNS disorders can be broadly classified into two types of drugs:
- Neurological disorders medicines (anti-Alzheimer's drugs, anti-parkinsonian drugs, antiepileptics drugs)
- Mental disorders medicines (antidepressants and antipsychotics drugs, Attention deficit hyperactivity syndrome (ADHD), insomnia and…)

CNS disorder medicines

Classification of Drugs Used to Treat CNS Disorders

Neurological Disorders		
Drugs	**Classification by Mechanism of Action**	**Leading Brands**
Anti-Alzheimers Drugs	Acetylcholinesterase Inhibitors	Aricept, Reminyl/Razadyne, Exelon
	N-methyl, D-aspartate Receptor Antagonists	Namenda, Ebixa, Axura
Anti-Parkinsonian Drugs	Dopaminergics	Madopar, Sinemet
	Dopamine Agonists	Mirapex, Cabser/Dostinex, Requip
	Catechol-o-methyltransferase inhibitors	Comtan, Stalevo
Antiepileptics	Traditional Anti-convulsants	Depakote/Valcote, Depakine,Tegretol
	Second Generation Anticonvulsants	Neurontin, Topamax, Lamictal
Pain Management Drugs	Non-steroidal Anti-inflammatory Drugs	Tylenol, Aspirin, Ultracet
	Opioids	Duragesic, Oxycontin, Sevorane/Ultane
Mental Disorders		
Antidepressants	Selective Serotonin Reuptake Inhibitors	Zoloft, Paxil, Lexapro
	Selective Norepinephrine Reuptake Inhibitors	Effexor, Remeron, Cymbalta
Antipsychotics	Typical Antipsychotics	Thorazine/ Largactil, Loxapac, Haldol, Phenotil
	Atypical Antipsychotics	Seroquel, Zyprexa, Risperdal, Abilify



Neurological Disorder medicines

Antiepileptics & Migraine medicines

- In epilepsy, a sedentary lifestyle due to regular seizures increases the risk of obesity. In addition, depression is common in people with epilepsy, which might contribute to the increased prevalence of obesity .
- Weight loss and weight gain induced by AEDs (Anti-Epileptic Drugs) may contribute to the important comorbidities of epilepsy, such as endocrine disturbance, risk and effects of seizure-related injuries.
- Medicines that stop migraine headaches and seizures affect hormones that control hunger and make it harder for body to sense when it's full.
- They can up patient's appetite, lower metabolism, and cause body to hang on to extra fluids. In one study, people who took valproic acid even had more fast-food cravings.

- Pharmacological treatment for epilepsy may be associated with substantial weight changes that may increase morbidity and impair adherence to the treatment regimen.
- Antiepileptic drugs (AEDs) that promote weight gain include **gabapentin**, **pregabalin**, **valproic acid**, and **vigabatrin** and possibly, **carbamazepine**.
- **Lamotrigine** and **levetiracetam** is an AED that is weight-neutral, while **topiramate** and **zonisamide** may induce weight loss.

Table 3. AEDs and effects on weight

Weight promoters Weight gain	Nonpromoters of weight gain Weight neutral	Weight loss
(Carbamazepine)		Felbamate
Gabapentin	Lamotrigine	Topiramate
Pregabalin	Levetiracetam	Zonisamide
Valproate	Phenytoin	
Vigabatrin		

Valproate

- Valproate is indicated for epilepsy and also for bipolar disorder and migraine prevention.
- Of the older AEDs, valproate is the one most recognized as causing weight gain. Of the newer AEDs, gabapentin, pregabalin, and vigabatrin have been shown in trials to cause weight gain.
- Besides obesity, endocrine disorders (hyperandrogenism,, menstrual disorders, anovulatory cycles, and polycystic ovary syndrome) have been reported in women receiving valproate therapy for epilepsy and it has been suggested that obesity-induced insulin resistance and hyperinsulinemia underlie these endocrine dysfunctions.

EXPERT REVIEWS

Weight change, genetics and antiepileptic drugs

Expert Rev. Clin. Pharmacol. 7(1), 43–51 (2014)

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Weight gain caused by antiepileptic drugs (AEDs) constitutes a serious problem in the management of people with epilepsy. AEDs associated with weight gain include sodium valproate, pregabalin and vigabatrin. Excessive weight gain can lead to non-compliance with treatment and to an exacerbation of obesity-related conditions. The mechanisms by which AEDs cause weight gain are not fully understood. It is likely that weight change induced by some AEDs has a genetic underpinning, and recent developments in DNA sequencing technology should speed the understanding, prediction and thus prevention of serious weight change associated with AEDs. This review focuses on the biology of obesity in the context of AEDs. Future directions in the investigations of the mechanism of weight change associated with these drugs and the use of such knowledge in tailoring the treatment of specific patient groups are explored.

KEYWORDS: epilepsy • genetics • obesity • pregabalin • sequencing • valproate • vigabatrin • weight

- VPA, a broad-spectrum AED used in the treatment of both generalized and partial seizures, has been reported to cause weight gain in up to 71% of exposed patients, although typically the rate is around 10%.
- Weight gain usually occurs within the first 3 months and peaks at 6 months after initiation of therapy.
- The degree of weight gain is variable, with about 10% of the patients experiencing severe weight gain.
- It has also been reported that **post-pubertal girls** are more likely to gain weight than post-pubertal boys or pre-pubertal children of any gender and that a longer duration of therapy correlates with weight gain.

- The mechanisms underscoring VPA-associated weight gain are diverse and numerous.
- 1- VPA therapy is associated with hyperinsulinemia, Insulin promotes glycogen storage in the liver and muscle and converts the excess glucose to fatty acids and triglycerides in the adipose tissue.
- 2- VPA therapy is also associated with hyperleptinemia and leptin resistance. A high soluble leptin receptor/leptin ratio has been observed in children with epilepsy. Serum leptin levels strongly correlate with BMI in children on VPA therapy. The relationship between increased leptin levels and increased BMI appears more marked in girls than in boys.
- 3- VPA therapy has also been associated with increased ghrelin levels at 6 months along with increased BMI in **prepubertal children**. Ghrelin is a peptide hormone secreted by the stomach and proximal small intestine. It is the only hormone known to stimulate appetite and promote food intake, resulting in a positive energy balance and weight gain.

- Adiponectin levels were lower (increase glucose) in obese epileptic patients when compared to those who did not gain weight.

Table 2. Reported possible molecular mechanisms of antiepileptic drug-induced weight change.

AED	Molecular mechanism	Ref.
Sodium valproate	GABA stimulation of the hypothalamus: increased	[24,109,110]
Sodium valproate	Hyperinsulinism and insulin resistance	[24,111–113]
Sodium valproate	Hyperleptinemia and leptin resistance	[112,114–116]
Sodium valproate	Leptin, ghrelin and adiponectin	[55,117,118]
Sodium valproate	Increased serum level of GLP-1	[119]
Pregabalin	Enhancement of GABA transmission	[106]
Topiramate	Increased expression of uncoupling proteins 1 & 2	[66,80,81,120–122]
Topiramate	Reduced serum galanin levels	[74]
Topiramate	Inhibition of mitochondrial carbonic anhydrase isoforms (VA and VB)	[123,124]
Topiramate	Stimulation of lipoprotein lipase in brown fat	[77–79]
Zonisamide	Inhibition of mitochondrial carbonic anhydrase isoforms (VA and VB)	[22,123–125]

AED: Antiepileptic drug.

Gabapentin

- GBP is a GABA analog that also acts on presynaptic calcium channels. It is used to help manage certain epileptic seizures and relieve pain for some conditions.
- A study involving 610 epilepsy patients on GBP as an add on therapy reported weight gain in 10% to 15% of patients, an effect that appeared dose dependent.
- The weight gain started after 2–3 months and tended to stabilize after 6–9 months.
- Edema has been attributed to gabapentin.
- It can also reduce the rate of metabolism.
- It increases hunger.
- Reduce level of energy and lack of motivation.

- Factors that may impact on weight gain by Gabapentin:

- **Duration of Intake**
- **Daily Routine**

Friends and family of the patient need to play an important role in this regard. They need to keep the patient motivated and on track for continuing a healthy daily routine.

- **Genetics**

Genes specifically control how a patient reacts psychologically to a certain medication. genes significantly control the weight changes in this scenario.

Pregabalin

- Pregabalin is used to treat epilepsy, neuropathic pain, fibromyalgia, restless leg syndrome, and generalized anxiety disorder.
- In one trial (epilepsy) showed that **12–14% weight gain** for those patients treated with **600 mg** of PGB compared with **10% gain** in those treated with **150 mg** and **6%** in the **placebo group**.
- This adverse drug reaction (ADR) is not associated with baseline BMI, gender or age.
- Although the exact mechanism of PGB-induced weight gain is unknown, enhancement of GABA transmission may play a role.

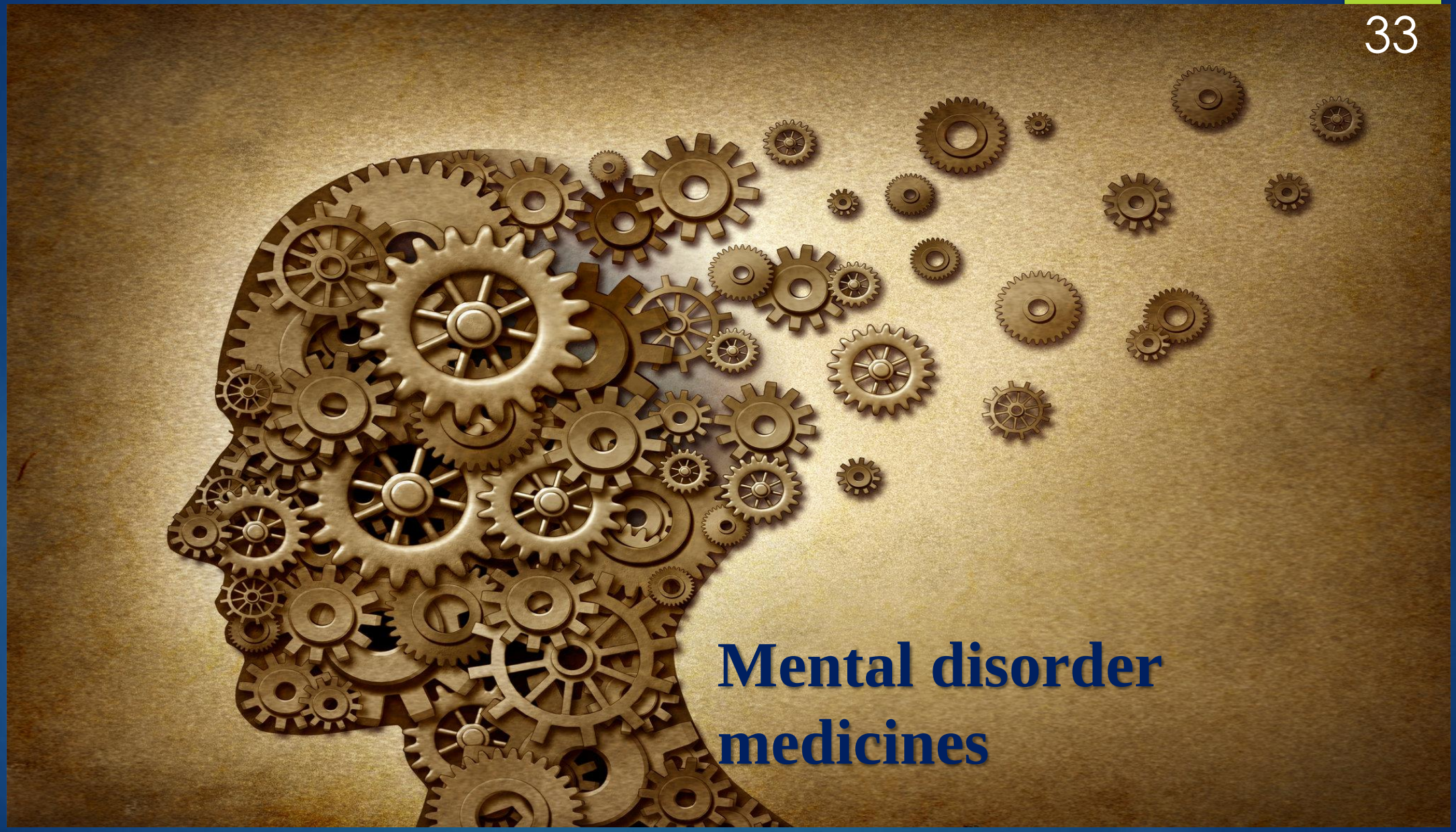
- In a different patient population comprising people with neuropathic pain, clinically relevant weight gain (>7% of baseline weight) was seen in11.4 % of the treatment group compared to 3.1% of the placebo group.

- A meta-analysis of pooled data from **106 studies** involving 43,525 patients treated with 150–600 mg of PGB indicates that the majority of patients maintained their weight within **7% of baseline weight.**

Carbamazepine

- CBZ is a sodium channel blocker and one of the most commonly prescribed AEDs. Weight gain has been reported in around 5% of individuals on CBZ treatment, an effect that appears idiosyncratic(influences weight by targeting adipocytes to alter adipose tissue metabolism and differentiation).
- **Increase appetite**
- **Excessive food intake**
- The worst weight gainers are adolescents, both male and female, in the age group of 10-20 years.
- The weight was successfully reduced by 8-10 kg by using acetazolamide which is also used in epilepsy in divided doses (8-30 mg/kg), without alterating seizure control or serum carbamazepine levels, in a period of 3-6 weeks.

- The mechanism of weight change effected by these AEDs is poorly understood, and may in large part have an underlying genetic basis.
- We should consider the potential effects of AEDs on weight when initiating treatment in an individual patient.
- For example, valproate should generally be avoided when initiating therapy in someone with epilepsy and co-morbid obesity, whereas ZNS would be best avoided in an individual with low body mass, or a history of anorexia.



Mental disorder medicines

Antidepressants

- These drugs help treat mental health conditions like bipolar disorder or schizophrenia. They "directly affect the brain and appetite and metabolism.
- Antidepressants consistently have a lower weight gain potential when compared to antipsychotics. However, antidepressants may carry a greater weight gain burden globally as they are prescribed more frequently than antipsychotics.
- Up to 25% of people who take antidepressants gain weight !
- It might be a situation where someone **feels so much better** when taking an antidepressant that lots of things suddenly start feeling more pleasurable to them, and food is just one of them. So in this instance they may actually be **overeating**.
- Antidepressants such as tricyclic antidepressants and monoamine oxidase (MAO) inhibitors are most often associated with significant weight gain. **Amitriptyline** is thought to induce **the most weight gain**.
- Some antidepressants may lead to weight gain by interfering with the neurotransmitter serotonin that may control appetite.

Older antidepressants, known as **tricyclic antidepressants** (TCAs) are notorious for increasing appetite and for causing weight gain. (**amitriptyline** and **nortriptyline**)
TCAs affect neurotransmitters in the brain and exhibit antihistamine activity, which can boost appetite and lead to weight gain. TCAs are also be used to treat migraine headaches.
One study show that during a planned 6-month treatment course of tricyclic antidepressants (TCA), 44% of patients on amitriptyline and 70% on nortriptyline stopped treatment due to excessive weight gain.

Many factors can contribute to weight gain during antidepressant therapy:

- Overeating or inactivity as a result of depression can cause weight gain.
- Some people lose weight as part of their depression. In turn, an improved appetite associated with improved mood may result in increased weight.
- Adults generally tend to gain weight as they age.

TCA

- The extent and probability of weight gain appears to differ substantially between individual TCA.
- Weight gain to be more pronounced with amitriptyline than with imipramine, or desipramine.
- During the first 6–9 months of continuous treatment, a constant monthly gain of 0.6–1.4 kg was observed.
- After discontinuation, body weight decreased, but remained above the normal level before disease onset.
- Stimulation or functional antagonism of dopamine, norepinephrine, serotonin and histamine receptors (Increased appetite, Increased risk for insulin resistance, Metabolic changes with increased risk of obesity)

Table 2. Liability and extent of weight gain during treatment with different TCA and zimelidine

Study	Sample	Design	Observation period	Effect
Fernstrom and Kupfer [146]	n = 73, depression	Open, randomized, prospective, inpatients	1 month	Amitriptyline: weight gain in 89%, mean +3.9 kg. Nortriptyline: weight gain in 66%, mean +2.2 kg. Desipramine: weight gain in 66%, mean +2.2 kg. Zimelidine: weight gain in 8%, mean +0.1 kg; weight loss in 22%, weight gain unrelated to effectiveness of treatment
Kazes et al. [78]	n = 35, unipolar or bipolar depression	Open, not randomized, prospective, in/outpatients	4–6 months	Weight gain of similar extent with amitriptyline, imipramine, clomipramine, maprotiline, reaching +2.5 kg at 6 weeks and +5.2 kg at 4–6 months. At 6 months weight gain >5 kg in 37%, >10 kg in 17% of patients. Weight gain unrelated to effectiveness of treatment
Frank et al. [147]	n = 115, depression	6 months initial open outpatient treatment, then double-blind, placebo-controlled, randomized outpatient maintenance treatment	3 years	During initial open imipramine treatment unspecified weight gain in 66% of patients. During maintenance treatment with imipramine weight gain by +2.6 kg, not different from +1.3 kg with placebo
Balon et al. [19]	n = 158 (panic disorder); n = 17 (depression)	Not randomized, retrospective, outpatients	up to 4 years	Liability of carbohydrate craving: Amitriptyline: 4/10 = 40%. Doxepin: 6/16 = 38%. Imipramine: 14/125 = 11%. Desipramine: 1/71 = 1.4%. Phenelzine: 1/22 = 4.5%

Weight effect	Antidepressants
Marked weight gain	amitriptyline,
	doxepin
	imipramine,
	clomipramine
	nortriptyline
Moderate weight gain	Desipramine
No data available	Trimipramine

- In one study body weight and appetite were evaluated in 40 depressed outpatients who were receiving TCAs.

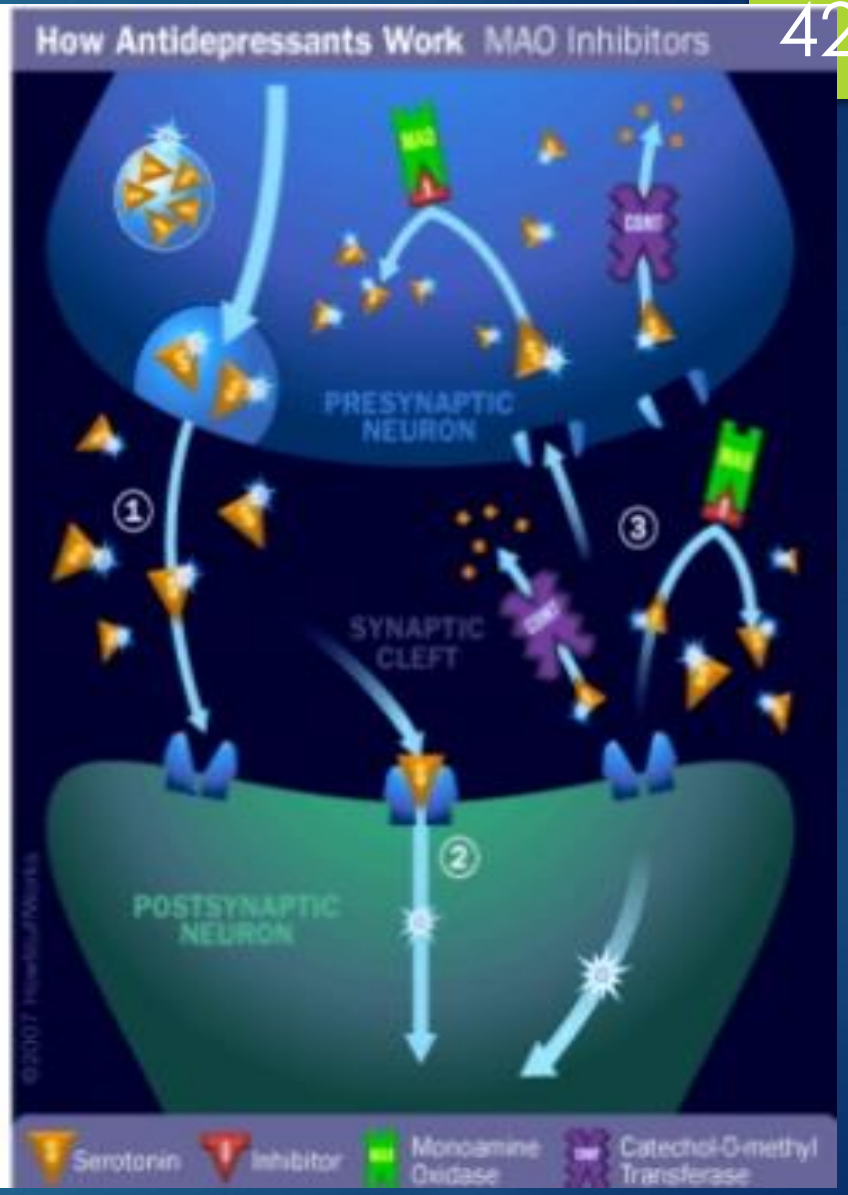
- Amitriptyline (maximum of 150 mg/day), nortriptyline (maximum of 50 mg/day), and imipramine (maximum of 80 mg/day) were given for an average of 6 months of treatment. There was a mean weight increase of 0.6-1.3 kg/month, which led to an average total weight gain of 1.5-7 kg, depending on drug, dose and duration. These weight increases were linear.

Table 1. Effect of psychotropic drugs on body weight

Weight effect	Antidepressants	Mood stabilizers	Antipsychotics	Other
Marked weight gain	amitriptyline, doxepin, imipramine, clomipramine, maprotiline, nortriptyline, mirtazapine	lithium, valproate	chlorpromazine, thioridazine, perphenazine, trifluoperazine, clozapine, olanzapine, zotepine, risperidone, sulpiride, quetiapine	
Moderate weight gain	paroxetine, desipramine, phenelzine	carbamazepine	haloperidol, fluphenazine, flupentixol, clopenthixol, fluspirilene	
No weight effect	fluoxetine, fluvoxamine, sertraline, citalopram, nefazodone, bupropion, venlafaxine, tianeptine, isocarboxazid, tranylcypromine	(lamotrigin, gabapentine, tiagabine)	amisulpride, ziprasidone, fluspirilene	benzodiazepines, anticholinergics, acamprosate
Weight loss	(only initially: SSRI)	topiramate, felbamate	molindone, pimozide	sibutramine
No data available	trimipramine, moclobemide, reboxetine			opipramol

How do MAOIs work

- Depression linked to an imbalance of chemicals within the brain.
- In brain there are chemical messengers\neurotransmitters, called monoamines- noradrenalin, serotonin.
- Neurotransmitters control or regulate bodily functions, & noradrenalin and serotonin control and regulate mood.
- During depression, there may be a decrease in amount of these monoamines released from nerve cells in the brain. Monoamines are broken down by an enzyme called monoamine oxidase.
- MAOIs prevent monoamine oxidase from breaking down the monoamines. This results in an increased amount of active monoamines in the brain.
- By increasing the amount, the imbalance of chemicals, important in causing depression, is altered. This helps relieve the symptoms of depression.
- Moclobemide is a more selective type of MAOI, called a reversible inhibitor of monoamine oxidase type A (RIMA).



MAOIs (Depression ,Panic & Parkinson's disease,….)

- Monoamine oxidase inhibitors (MAOIs) are less likely to produce weight gain than TCA.
- Use of MAOI typically requires diet restrictions because they can cause dangerously high blood pressure when taken with certain foods or medications.
- Phenelzine elicits the greatest amount of weight gain (comparable to imipramine)
- Isocarboxazid is reported to cause minor weight gain and even weight loss.
- There are no cases of tranylcypromine-induced weight gain in the literature.
- Appetite control may be affected by MAOIs (probably have different effects on the mechanisms of appetite control)

Newer and Older MAOIs

MAOIs had been reserved as a last line of RX.

MAOIs available at present can be classified into 3 types:

- Older, irreversible nonselective (first generation) : phenelzine, tranylcypromine and isocarboxazid
- Irreversible, selective drugs (second generation) : selegiline
- Reversible, selective drugs (third generation) : (moclobemide),This latter group of drugs are also known as RIMAs (reversible inhibitors of MAO-A), effective treatments for depression/ first-line.

SSRI

- Another class of antidepressants, called **selective serotonin reuptake inhibitor** (SSRI), are not always linked with weight gain, but some frequently prescribed SSRIs, like **paroxetine**, can cause weight gain. **Fluvoxamine** has also been tied to weight gain. Some SSRIs are more weight neutral, such as fluoxetine, citalopram, escitalopram or sertraline.
- In contrast to TCA, SSRI were thought to induce weight loss rather than weight gain.
- The SSRI paroxetine is the worst offender, the antidepressant most likely to cause weight gain, while another SSRI, sertraline, is the least likely, so that's a switch that can sometimes make a big difference for some people.
- Paroxetine is most commonly associated with weight gain with both long-term and short-term use.
- Long-term use of the SSRIs may cause weight gain (longer than 6 months).

- Weight gain is also less likely to occur with the following SSRIs when they're used for less than six months:

Paroxetine, Sertraline, Fluoxetine & Citalopram

- Although some SSRIs are associated with weight loss at first, long-term use of SSRIs is mostly linked to weight gain.
- There are a number of studies on the effect on body weight of fluoxetine in patients without psychiatric disorders treated for extreme obesity, in patients with bulimia nervosa, and in subjects stopping cigarette smoking.
- Some people may gain weight while taking Prozac simply because they were not eating well while they were depressed and the antidepressant has caused their normal appetite to return.


Other
Antidepressants
MIRTAZAPINE

- **Mirtazapine** is an antidepressant that boosts serotonin, like SSRIs, but also has an antihistamine effect that may lead to weight gain (Appetite increase).
- Mirtazapine is less likely to make people gain weight compared with TCAs.
- In one study, increased appetite was found in 24% of patients treated with mirtazapine compared to 6% treated with trazodone and 4% with placebo.
- Weight gain might be at the first weeks of treatment with body weight reaching a plateau after 2 months despite ongoing treatment.

- **Bupropion** is antidepressant that is actually associated with weight loss, and it's also an antidepressant linked with less sexual side effects.
- **Venlafaxine** and **duloxetine** also have more neutral effects on weight gain.
- They are antidepressant medications of the serotonin-norepinephrine reuptake inhibitor(SNRI) class.
- For venlafaxine, this is somewhat surprising given the structural relationship to sibutramine, which effectively reduces body weight and is licensed for treatment of morbid obesity in several countries.

Antidepressants that don’t cause weight gain

- Escitalopram (SSRI)
- Duloxetine (SNRI)
- Bupropion (atypical antidepressant)
- Venlafaxine (SNRI)
- Selegiline (MAOIs),


ANTIPSYCHOTIC

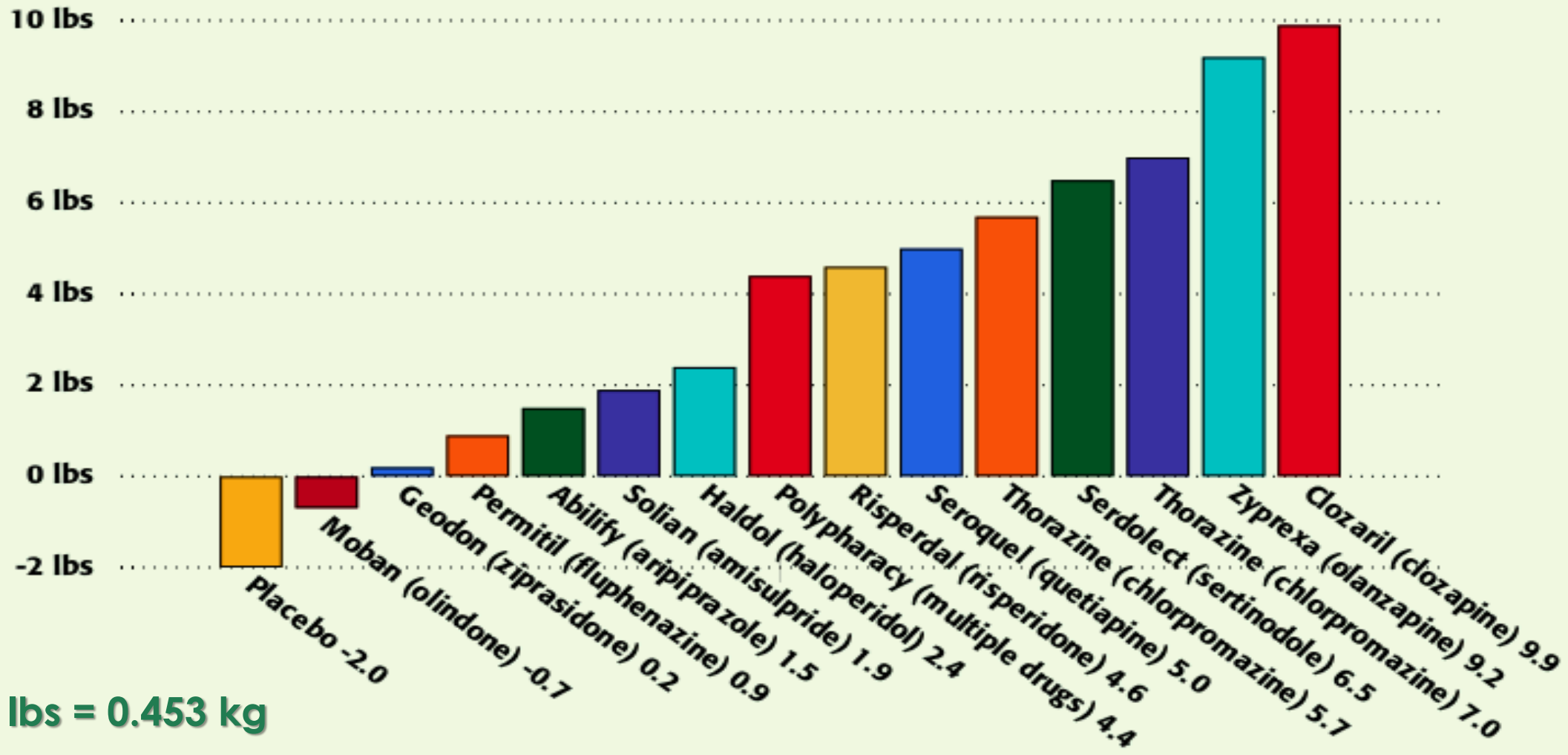
Classification of antipsychotic drugs

- **PHARMACOLOGICAL CLASSIFICATION**
  - **FIRST-GENERATION ANTIPSYCHOTIC (low potency)**
    - ***Chlorpromazine***
    - *Prochlorperazine*
    - *Thioridazine*
  - **FIRST-GENERATION ANTIPSYCHOTIC (high potency)**
    - ***Fluphenazine***
    - ***Haloperidol***
    - *Pimozide*
    - *Thiothixene*
  - **SECOND GENERATION ANTIPSYCHOTIC**
    - *Aripiprazole*
    - *Asenapine*
    - ***Clozapine***
    - *Iloperidone*
    - *Lurasidone*
    - ***Olanzapine***
    - ***Quetiapine***
    - *Paliperidone*
    - ***Risperidone***
    - *Ziprasidone*

Antipsychotics are frequently linked with weight gain:

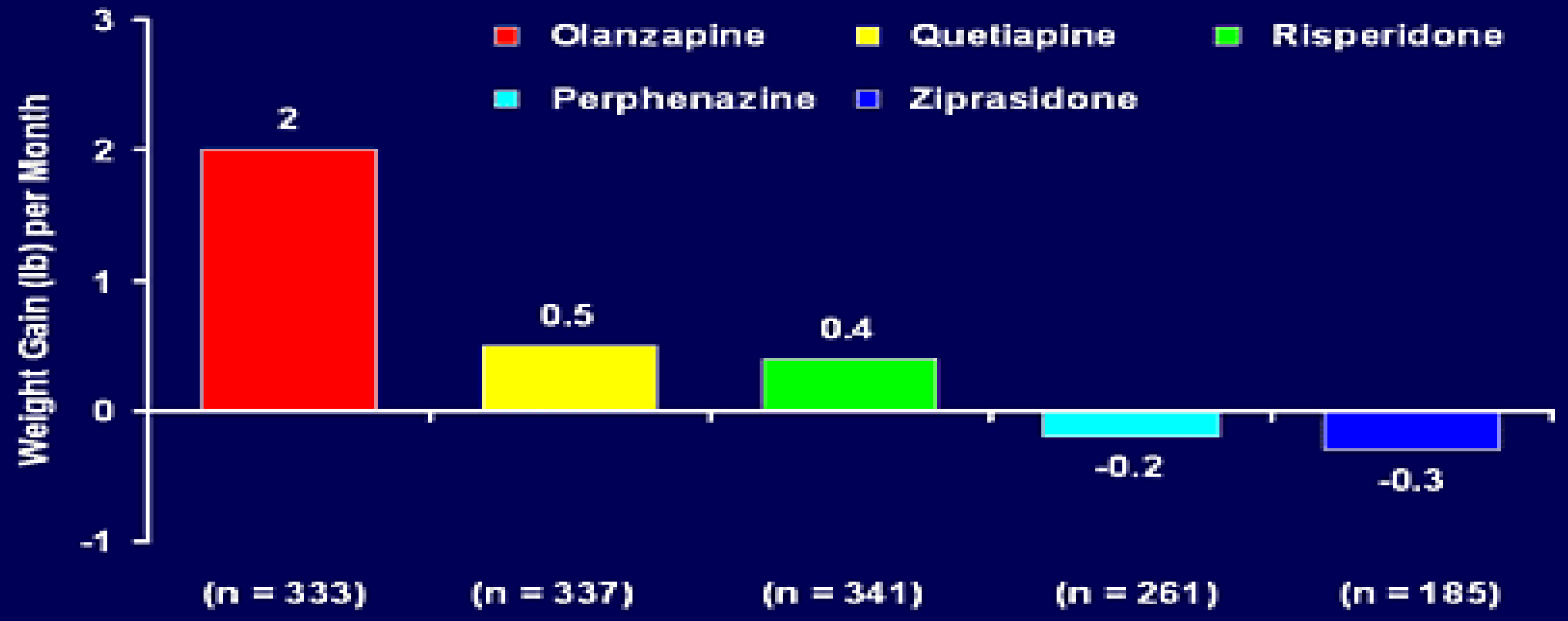
- **Atypical antipsychotics**: **olanzapine**, **risperidone** and **Clozapine**
- Patients may gain from 7% to 10% of their body weight by clozapine.
- These drugs may have antihistamine activity and also block serotonin, which may boosts appetite and lead to weight gain.
- **Older "typical" antipsychotics**: **haloperiodol**, **chlorpromazine** and **thioridazine** can also cause weight gain, but these drugs are used less frequently due to movement disorder side effects.
- Many of the antipsychotics may impair glucose (sugar) control and lead to insulin resistance, impaired glucose tolerance and **type 2 diabetes**.

Weight Gain from Antipsychotic Drugs after 2.5 Months



1 lbs = 0.453 kg

CATIE Trial Results: *Weight Gain per Month Treatment*



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

Antipsychotics and mood stabilizers

- Patients with mental health disorders are two to three times more likely to develop obesity than the general population.
- These drugs impair glucose metabolism, increase cholesterol and triglyceride levels and cause arterial hypertension, leading to metabolic syndrome.
- Metabolic syndrome will increase the risk of diabetes mellitus by five times and cardiovascular illness by two times over the next 5–10 years.
- Prevalence of metabolic syndrome is high in schizophrenia.
- A meta-analysis of 77 publications reported an overall rate of 32.5%

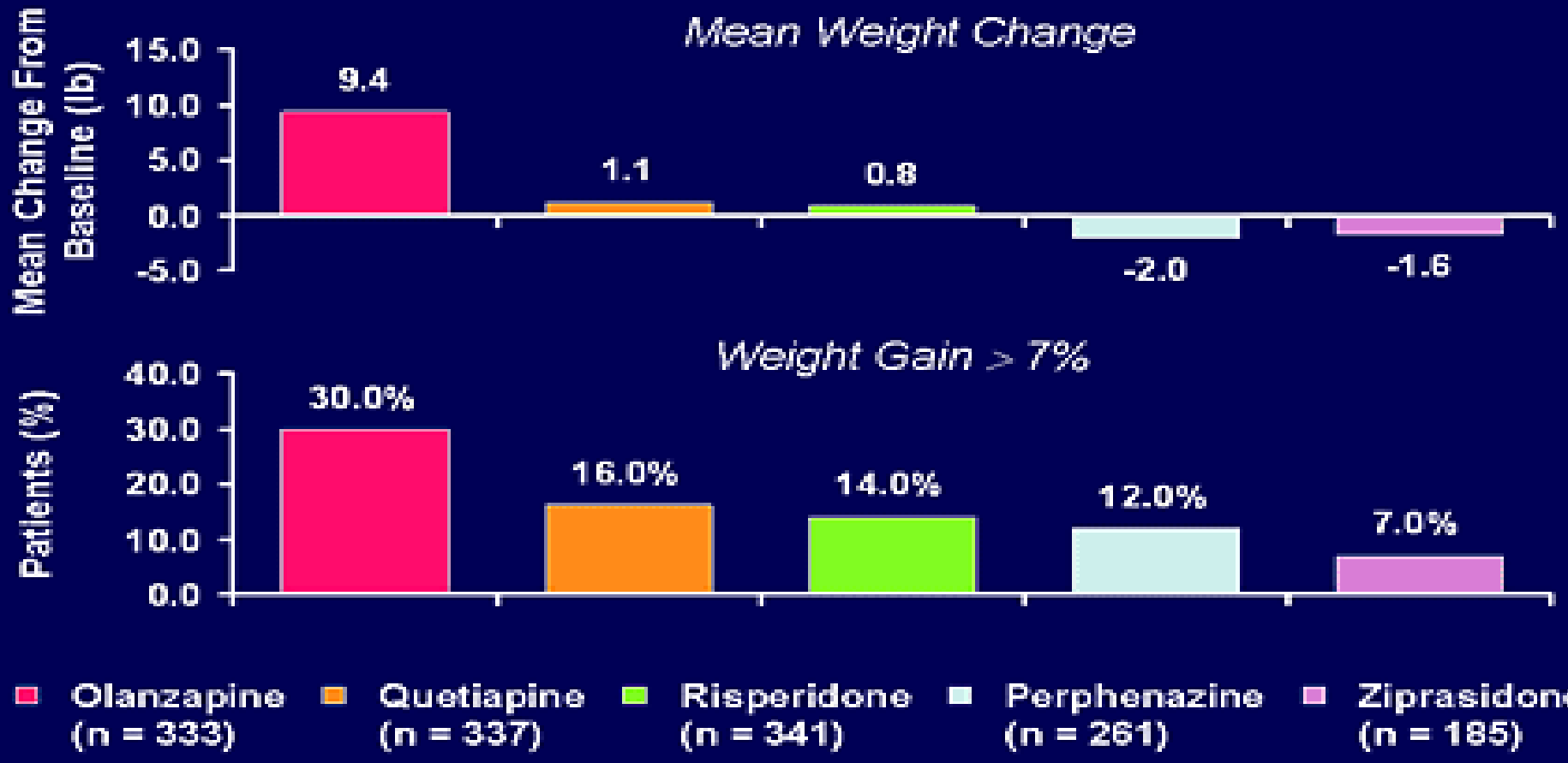
- Studies report that, on average, 29%–89%-of patients receiving clozapine will gain some weight and 8%–37% of patients taking olanzapine will gain ≥7% of their body weight.
- Aside from clozapine and olanzapine, commonly prescribed medications for schizophrenia such as chlorpromazine (0.6–15.9 kg), quetiapine (–1.5 to +4.1 kg), haloperidol (–0.1 to +4.0 kg) and risperidone (0.4–2.1 kg) are also reported to elicit significant weight gain.
- Aripiprazole (–1.4 to +0.2 kg) is associated with the least amount of weight gain among medications for schizophrenia, and thus, may be a more weight-favorable alternative.

Table 1 Likelihood of weight gain with antipsychotics

Antipsychotic	Propensity to cause weight gain
Clozapine	High
Olanzapine	High[a,b]
Chlorpromazine	Moderate
Quetiapine	Moderate[b]
Risperidone	Moderate[b]
Paliperidone	Moderate
Aripiprazole	Low[c]
Amisulpride	Low[c]
Asenapine	Low
Haloperidol	Low[d]
Ziprasidone	Low[c,d]
Lurasidone	Low[d]

Notes: [a]Significantly greater increase in weight at >38 weeks, when compared with <6 weeks period in both antipsychotic previously prescribed and naïve groups in the meta-analysis by Bak et al.[13] [b]Significant weight gain seen in antipsychotic naïve group even <6 weeks in the meta-analysis by Bak et al.[13] [c]Weight neutral with duration of antipsychotic use in the meta-analysis by Bak et al.[13] [d]No significant difference in weight when compared with placebo in multiple treatment meta-analysis by Leucht et al.[10] Data from studies.[9–11,13]

Outcome Measures of Safety: *Weight*



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

Mechanisms underlying weight gain caused by antipsychotics

- Clozapine, a second-generation antipsychotic, has affinity on many receptors including dopamine (DA), serotonin (5HT), muscarinic (M), histamine (H), adrenergic, GABAergic and glutamatergic receptors to mention a few. This poly-receptor profile activity is believed to account not only for its unique efficacy but also for the side effects including weight gain and weight loss.

- Antipsychotics affect neuropeptides associated with appetite control and energy metabolism.

- Antipsychotics that have less affinity to or have agonist activity are associated with less weight gain.

- Clozapine, the medication with the highest risk of weight gain, is also the only antipsychotic so far licensed for treatment of resistant schizophrenia.
- Patient demographics are an important consideration because differences in age, sex, BMI and so on may have a significant impact on the weight changes that occur.
- Weight gains associated with lithium are more severe in patients with obesity than their lower-weight counterparts (6.1 kg obese vs 1.1 kg non-obese).
- Conversely, the weight gains associated with olanzapine are lower with increasing body mass index.

- It is estimated that up to a third of those who are started on clozapine are already obese and that women may be more vulnerable.
- A meta-analysis on the metabolic effects of antipsychotics showed that clozapine and olanzapine caused more weight gain than other antipsychotics with rapid weight gain in the first few weeks that plateaued around 42–46 months for clozapine.
- A small number of patients lose weight following its use. Weight loss was as a result of improved mental state, better side-effect management and engagement in diet and exercise and genetic factor.
- Weight loss **early** on following clozapine use was associated with a **poor response to treatment**. Weight loss may be the early visible sign of a poor response to clozapine.

- In the case of **clozapine**, adding compounds that are known to induce weight loss such as topiramate, aripiprazole and metformin are options that can be considered if switching to other antipsychotics is not possible.

- **Aripiprazole** has agonist effect on serotonin resulting in reduced appetite. Topiramate inhibits lipogenesis peripherally. Centrally it increases satiety and hence reduces appetite.

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Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: Findings of a randomized clinical trial in a drug-naïve population ☆

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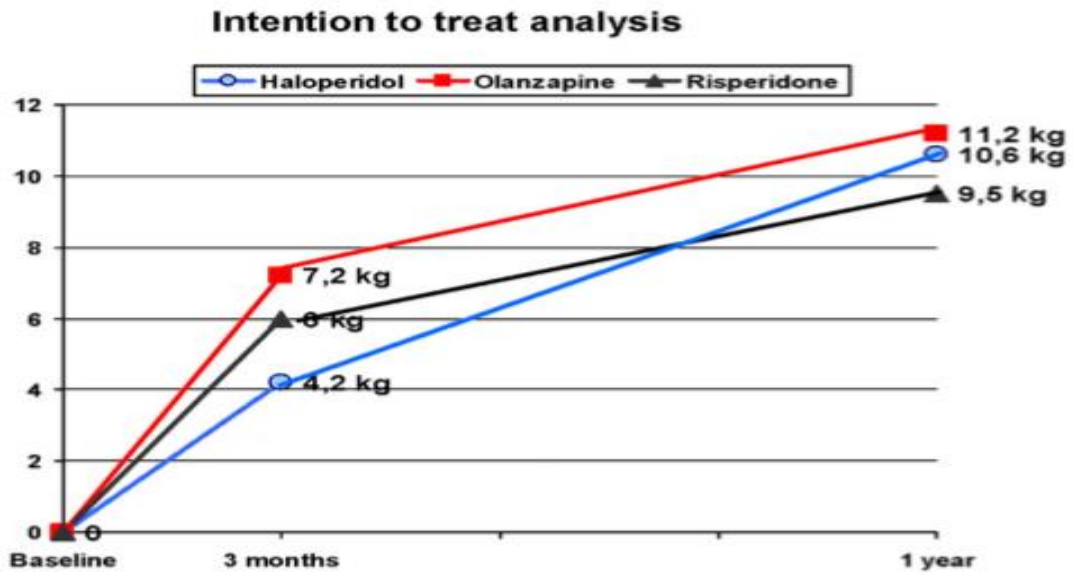
Received 24 July 2007; received in revised form 17 September 2007; accepted 18 October 2007
Available online 3 December 2007

Abstract

Background: There is little information about weight gain induced by antipsychotics at long-term.
Objective: To quantify the weight gain induced by first (haloperidol) and second generation antipsychotics (olanzapine and risperidone) in a cohort of drug-naïve subjects after 1 year of treatment.
Methods: This is a prospective, randomized clinical trial, including a representative sample of first episode psychotic incident cases from a population area of 555.000 people. The main outcome measures were changes in body weight and body mass index at 3 months and at 12 months. Both a per protocol analysis and an intention to treat analysis were conducted.
Results: A total of 164 drug-naïve patients were included. At 12 months 144 patients were evaluated. Of them, 66% completed the protocol and 34% needed treatment switch. We found statistically significant differences in weight gain at 3 months: 3.8 kg (±4.1) for haloperidol, 5.9 kg (±5.1) for risperidone and 8.4 kg (±5.0) for olanzapine ($F=7.045$; $p=0.002$). After 1 year the difference in weight gain had disappeared: 9.7 kg (±5.7) for haloperidol, 8.9 kg (±8.8) for risperidone and 10.9 kg (±7.2) for olanzapine ($F=0.817$; $p=0.445$).
Conclusions: Drug-naïve patients experience an extraordinary weight gain after 1 year of treatment with haloperidol, olanzapine or risperidone. The main difference among these treatments is the pattern of weight gain but not the final amount of weight gain.

Keywords: Weight gain; Long-term; Antipsychotics; First episode psychosis; Olanzapine; Risperidone; Haloperidol



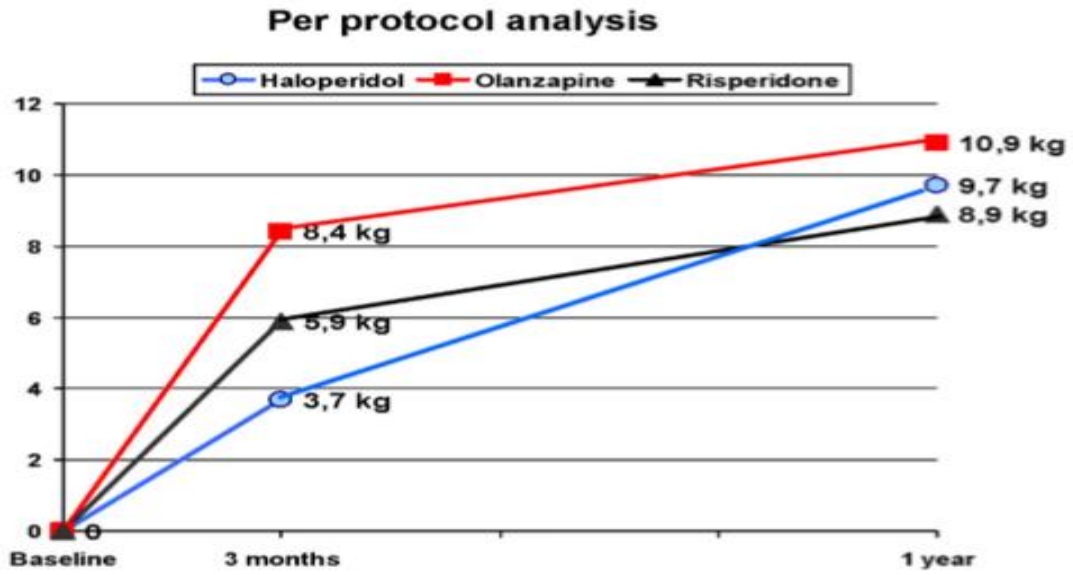
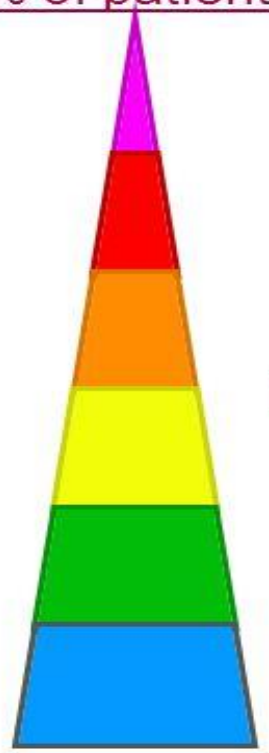


Fig. 2. Different patterns of weight gain after 1 year of treatment with haloperidol, olanzapine or risperidone in a population of drug-naïve psychotic patients.

Relative Risk of Weight Gain

78.8% of patients receiving antipsychotics increase baseline weight by >7%



Low

Moderate

High

- Ziprasidone (Geodon)
- Aripiprazole (Abilify)
- Risperidone (Risperdal)
- Quetiapine (Seroquel)
- Olanzapine (Zyprexa)
- Clozapine (Clozapine)

Wu Ren-Rong et al. JAMA 2008, Brooks JO et al. Current Psych Reports 2009

Timeline for weight gain

- There is rapid weight gain in the first few weeks after commencing antipsychotics.
- The rate of weight gain then gradually decreases and flattens over several months. Time taken to plateau was different for each antipsychotic, ranging from 4 to 9 months for **olanzapine** and from 42 to 46 months for **clozapine**.
- This indicates that patients would continue to gain weight for 1–4 years. It is consistently reported that patients continue to gain weight over time.
- Factors associated with rapid weight gain in the initial period were younger age, lower baseline BMI, more robust response to antipsychotic and increase in appetite. Rapid weight gain of more than 5% in the first month is the best predictor for significant long-term weight gain.

Strategies for Control of Antipsychotic Induced Weight Gain (AIWG)

Nonpharmacological:

- Lifestyle modification
- Dietary counseling
- Exercise interventions

- A meta-analysis of 10 RCTs which employed the nonpharmacologic interventions consisting of cognitive-behavioral interventions, nutritional counseling and combined nutritional and exercise interventions reported weighted mean difference of **-2.56 kg**. Nonpharmacologic interventions are important in the management of AIWG.

Pharmacological:

- Reducing the dose of the offending medication
- Switching to another antipsychotic with less potential of weight gain
- Adding an adjuvant to reduce weight
- A meta-analysis of RCTs of behavioral and pharmacologic interventions reported that short-term modest weight loss is possible with nonpharmacologic and selective pharmacologic interventions.
- A meta-analysis of 40 trials reported that **metformin** was the most extensively studied drug. It was observed that adjunctive medications were initiated simultaneously with antipsychotics in 13 studies (26%).
- The adjunctive treatment for weight gain was mostly initiated when nonpharmacologic interventions alone were not sufficient or impractical and switching antipsychotics was not practicable.
- **Metformin** has the most evidence of efficacy, while topiramate, sibutramine and aripiprazole are also effective. These drugs prevent or treat weight gain through different mechanisms.

- **Metformin:** The main mechanism of weight loss may be by reduction of insulin resistance and suppression of appetite and glycemic control, are also an advantage.

- A recent meta-analysis of 12 studies reported a -3.27 kg mean change in weight between metformin and placebo. The dose used in the trials ranged from 750 to 1,500 mg/day.

- **Aripiprazole:** Meta-analysis of three RCTs of aripiprazole as an add-on weight-reducing agent reported a mean difference of -2.13 kg compared to placebo. In addition to weight loss, significant reduction in total and low-density lipoprotein cholesterol was observed in the aripiprazole group. The other advantage is that aripiprazole is an antipsychotic.

When to Consider Metformin

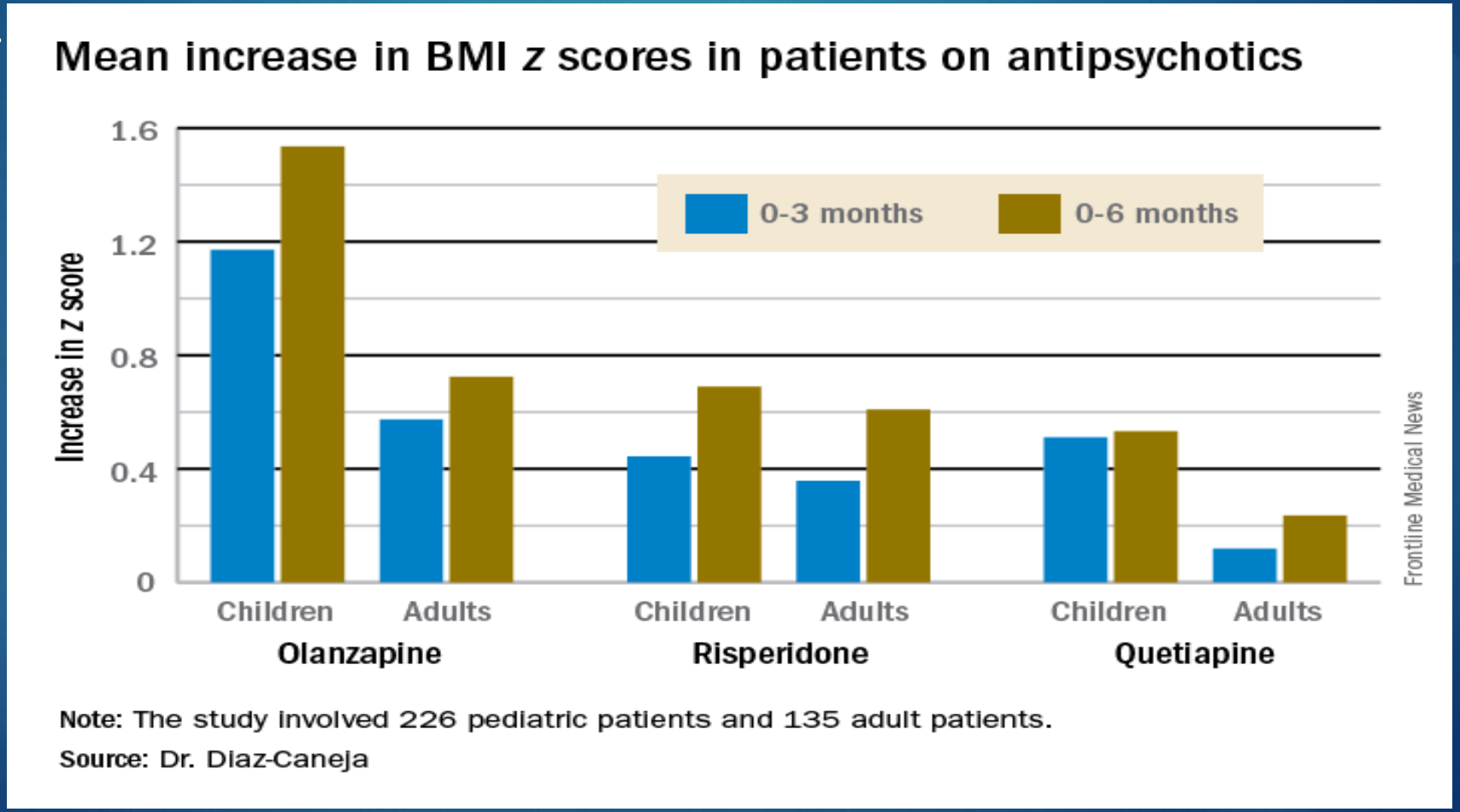
- > 7% weight gain over baseline
- Good renal function - stable
- Positive antipsychotic response requires ongoing treatment

- Orlistat acts at a peripheral level by inhibiting lipase and thereby reducing intestinal absorption of fat by 30%. In combination with a weight-reduction program, a mean weight loss of 5% within 24 weeks could be achieved.
- Adding fluvoxamine to clozapine actually worsens weight gain compared to clozapine alone. Therefore, adding serotonergic drugs (SSRI) does not appear helpful in managing untoward weight gain.

- Antipsychotic switching is one strategy that can be employed to reduce weight.
- Medication switching should be carried out after careful consideration of the risk of relapse and this should be done in consultation with the patient.
- The possibility of causing more weight gain must also be considered when switching medication.
- **Haloperidol** and **aripiprazole** are considered the best options according to evidence from meta-analyses.
- A Cochrane Review of four RCTs reported a mean weight loss of 1.94 kg when patients were **switched from olanzapine to aripiprazole or quetiapine**.
- For many mental health disorders, drug treatment may be absolutely necessary and the risk of stopping the drug may be greater than the risk associated with weight gain.

AIWG in children and adolescents

- Weight gain is one of the most troublesome side effects in children, with up to 80% of children showing significant weight gain.
- More weight gain had been observed in adolescent patients than in older patients.



Mood stabilizer Drugs

CLASSIFICATION

- Lithium
- Anticonvulsants
1. Carbamazepine
2. Divalproex
3. Lamotrigine
- Typical antipsychotics
1. Chlorpromazine
2. Haloperidol

- Atypical Antipsychotics
1. Aripiprazole
2. Lurasidone
3. Olanzapine
4. Olanzapine+fluoxetine
5. Quetiapine
6. Risperidone
7. Ziprasidone
8. Asenapine

Lithium

- **Lithium** is commonly prescribed for the treatment of bipolar disorders.
- The mean extent differs between studies, ranging from 5kg within 2 years in 11% of all patients up to 10kg in two thirds of patients after several years and can go up to 30kg in individual patients.
- Clinically relevant obesity was found in 20–25% of patients after several years of lithium treatment.
- Weight gain appears to occur mainly within the first 2 years and then levels off despite continuous intake.
- Women are thought to be more severely affected.
- Patients with pre-existing high body weight are at increased risk for lithium induced further weight gain.
- Mood stabilizers cause patient's appetite to turn on and stay on. Some may cause as much as an 5 kg weight gain in 10 weeks.

Hormonal Medicines

Hormonal Contraceptives

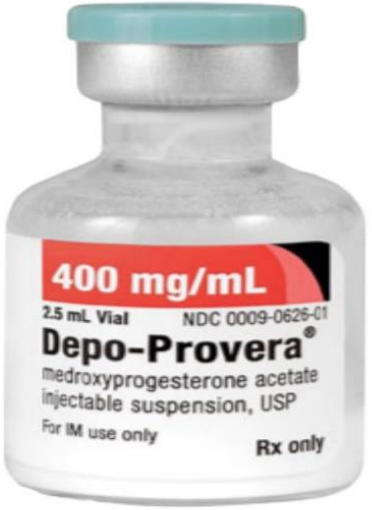
Hormonal contraception refers to birth control methods that act on the endocrine system with steroid hormones.

There are two main types of hormonal contraceptive formulations:

- Combined Oral Contraceptive pills (COCs) which contain both an estrogen and a progestin
- Progestogen-only Oral Contraceptive pills which contain only progesterone or one of its synthetic analogues (progestins) used as injection like Depo Provera and implants.

- In general, the birth control pill is not usually associated with weight gain, especially the newer pills with lower doses of estrogen and progestin.
- One form of birth control, the birth control shot known as **medroxyprogesterone** (**Depo-Provera**) that is given every 3 months, can cause **significant weight gain** in some women.
- A review of 44 studies showed no evidence that birth control pills caused weight gain in most women. And, as with other possible side effects of the pill, any weight gain is generally minimal and goes away within 2 to 3 months.

- When birth control pills were first sold in the early 1960s, they had very high levels of estrogen and progestin (contained 150 mcg of the estrogen mestranol). Today's pills only contain 20 to 50 mcg of estrogen.
- Estrogen in high doses can cause weight gain due to increased appetite and fluid retention. So, 60 years ago they may indeed have caused weight gain in some women.
- Current birth control pills have much lower amounts of hormones. So weight gain is not likely to be a problem. some people may be more prone to weight gain than others.
- Users who rapidly gain weight initially may also be at higher risk of greater weight increase.
- Long-acting injectable depot medroxyprogesterone acetate (**Depo-Provera**) is the **only** hormonal contraceptive that is consistently associated with **weight gain**. A prospective study found that women who used Depo-Provera gained an average of (5.1 kg) over 36 months, whereas women who used combined oral contraceptives did not gain any weight.



Depo-Provera and weight gain

Depo-Provera (DPMA) : is an injectable birth control containing progestin. It must be administered by a doctor every three months

what we know

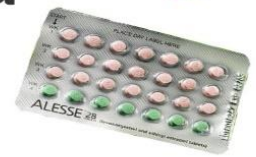
DMPA is directly correlated with significant weight gain and increased body fat.

why the weight gain?

- DMPA has higher does of progesterone
- extra hormones could slow your metabolism, promote fat storage, or increase appetite

after stopping DPMA, the majority of participants lost any weight they gained on the shot

your other options



what to do if weight gain is a concern for you

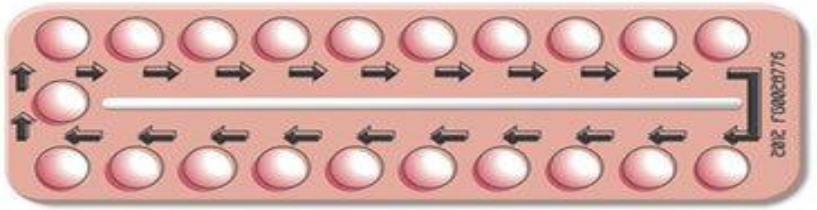
- stop DMPA
- switch contraceptive methods
- pay close attention to diet and exercise
- examine lifestyle choices that could influence weight gain

always consult your healthcare provider before stopping or altering your birth control method or your normal diet and exercise routines

Changes in hormone levels during:

- Puberty : Increase in estrogen that causes body fat to be deposited.
- Menopause : hormonal changes that causes an increase in body fat, particularly around the abdomen.
- Hormones also likely impact food intake.
- A systematic review published in 2004 (47 RCT) concluded that women using COCs gain no more weight than nonhormonal user controls or other contraceptive method users.
- Other studies evaluated reported a slight increase in weight of approximately 0.5 kg but less than 2 kg.
- This is often temporary and the result of water retention, not actual weight gain(It isn't actual fat gain).

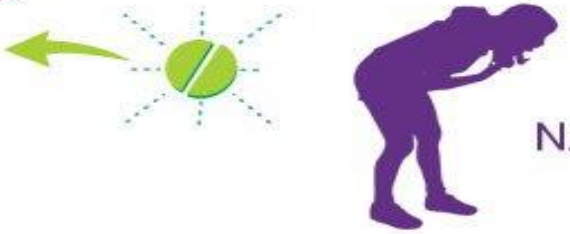
10 SIDE EFFECTS OF



BIRTH CONTROL PILLS

THAT YOUR DOCTOR MAY NOT TELL YOU

HEADACHES & MIGRAINES



NAUSEA

BREAST TENDERNESS

BREAKTHROUGH BLEEDING

WEIGHT GAIN

- YEAST INFECTIONS
- VISUAL CHANGES
- BLOOD CLOTS
- MOOD CHANGES
- DECREASED LIBIDO

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Mechanism of Weight Change in Combined Contraceptive Users

- There are several possible mechanisms in which weight gain could occur as a result of COC use. **Increased appetite** could result from a suppression of serum cholecystokinin.

- It is suggested that estrogen in COCs causes **fluid-retention** weight gain by direct stimulation of the renin–angiotensin system, which can lead to water retention, which in turn leads to sodium retention.
- Lower dose COCs reduce fluid retention.


CORTICOSTEROIDS

Corticosteroids

- Cortisol is a hormone made by the adrenal glands.
- **Corticosteroids** are synthetic analogues of human hormones normally produced by the adrenal cortex.
- They have both glucocorticoid and mineralocorticoid properties.
- The glucocortoid components are antiinflammatory, immunosuppressive, anti-proliferative and vasoconstrictive. They influence the metabolism of carbohydrate and protein may cause DM and osteoporosis.
- Mineralocorticoid's main significance is in the balance of salt and water concentrations. Due to the combination of these effects, corticosteroids can cause many adverse effects like water retention and hypertension.
- According to one study, weight gain was the most commonly reported adverse effect of steroid use, affecting 70 percent of those prescribed the drugs.

- Oral corticosteroids are absorbed systemically and are therefore more likely to cause adverse effects than topical or inhaled corticosteroids.

- When taken orally, powerful anti-inflammatory agents such as prednisone, methylprednisolone and hydrocortisone can cause insulin resistance, elevated blood glucose levels and ultimately more fat storage.

- Greater duration of treatment will lead to a greater number of adverse effects, and therefore the most at risk group are those taking high dose, long-term oral corticosteroids (**LTOC**).

- High dose is defined as a prescription of >5 mg oral prednisolone and long term as duration of treatment >1 month

- Steroids can affect the metabolic rate, and lead to increased appetite and overeating and fatty tissue increases which can cause an increase in the abdomen size.
- At first, weight gain will be due to water retention. But over time, body fat may increase as well.

- Short-term use of corticosteroids has not been shown to be associated with significant changes in body weight.
- Conversely, literature on the long-term usage (≥3 months) of corticosteroids suggests the opposite, with prednisone (1.7–5.8 kg), prednisolone (1.5–4.4 kg) and cortisone (1.5–8.4 kg) being associated with **significant weight gains**.

Drug name	Weight effect
Cortisone[187–189]	++
Prednisolone[185,186]	++
Prednisone[182–184]	++

Treatment-emergent weight changes associated with corticosteroids
Notes: +=>1 kg. Additional + refers to **≥3 kg** weight change.

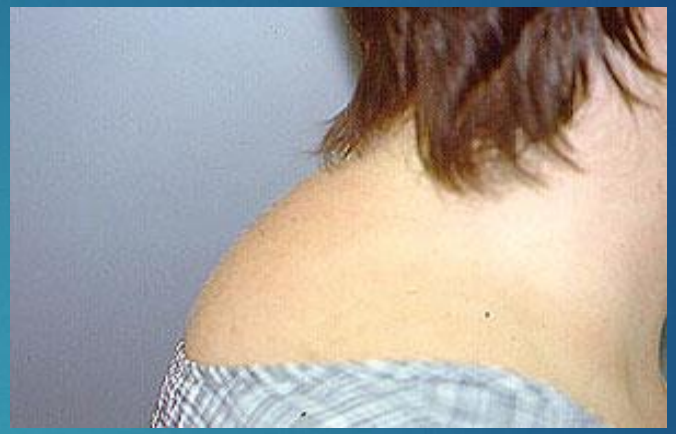
These factors contribute to weight gain by causing:

- Increased appetite
- Fluid retention
- Changes in where the body stores fat

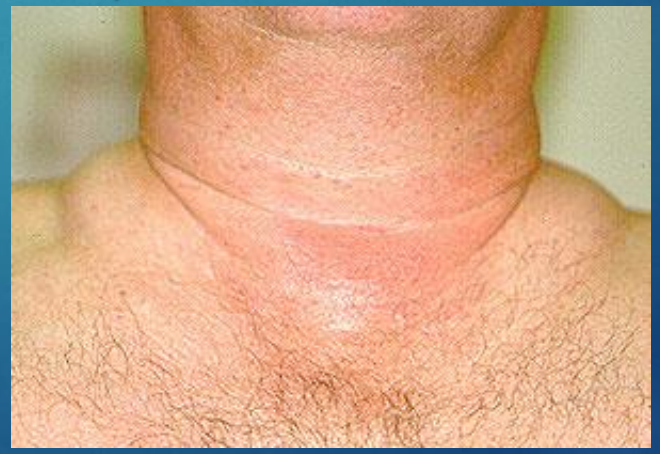
- Many people on steroids notice increased fat in the abdomen, face, and neck.
- The amount of weight gain varies from individual to individual. In addition to causing weight gain, prednisone leads to a ***redistribution* of body fat** to places that are undesirable, particularly the face, back of the neck, and abdomen.

- Prolonged use, especially of oral corticosteroids, is notorious for inducing hypercortisolism related side effects and is archetypal for exogenous Cushing's syndrome.

- **Pictured below** is a example of redistribution of body fat to the back of the neck. Accumulation of fat in this area is sometimes referred to as a "buffalo hump".



Supraclavical "fat pads" are collections of fat at the base of the neck, which are common in patients on steroids. They sometimes cause concern among patients if mistaken for lymph nodes or other causes for worry, but will gradually subside as the prednisone dose is tapered to below 10 milligrams/day.



Danazol

Danazol is a derivative of the synthetic steroid ethisterone, a **modified testosterone**.

- Androgenic hormone (anabolic and androgenic activities)
- Danazol has antigonadotropic and anti-estrogenic activities. Danazol acts as an anterior pituitary suppressant by inhibiting the pituitary output of gonadotropins.
- Decrease in fat and increase in lean tissue is likely to be a predominantly androgenic effect.
- In one study after 6 months, there was a significant increase in lean tissue mass. Body fat decreased thus has both anabolic and androgenic effects on body composition.

Aromatase Inhibitors

- **Aromatase inhibitors (AIs)** are a class of drugs used in the treatment of breast cancer in postmenopausal women and gynecomastia in men.
- Aromatase is the enzyme that catalyzes a key aromatization step in the synthesis of estrogen.
- As breast and ovarian cancers require estrogen to grow, AIs are taken to either block the production of estrogen or block the action of estrogen on receptors.
- Aromatase inhibitors are generally not used to treat breast cancer in premenopausal women.

There are two types of aromatase inhibitors approved to treat breast cancer:

- Irreversible steroidal inhibitors, such as exemestane (Aromasin), forms a permanent and deactivating bond with the aromatase enzyme.
- Nonsteroidal inhibitors, such as anastrozole (Arimidex) and letrozole (Femara), inhibit the synthesis of estrogen via reversible competition for the aromatase enzyme.
- In one study weight gain was 14%.