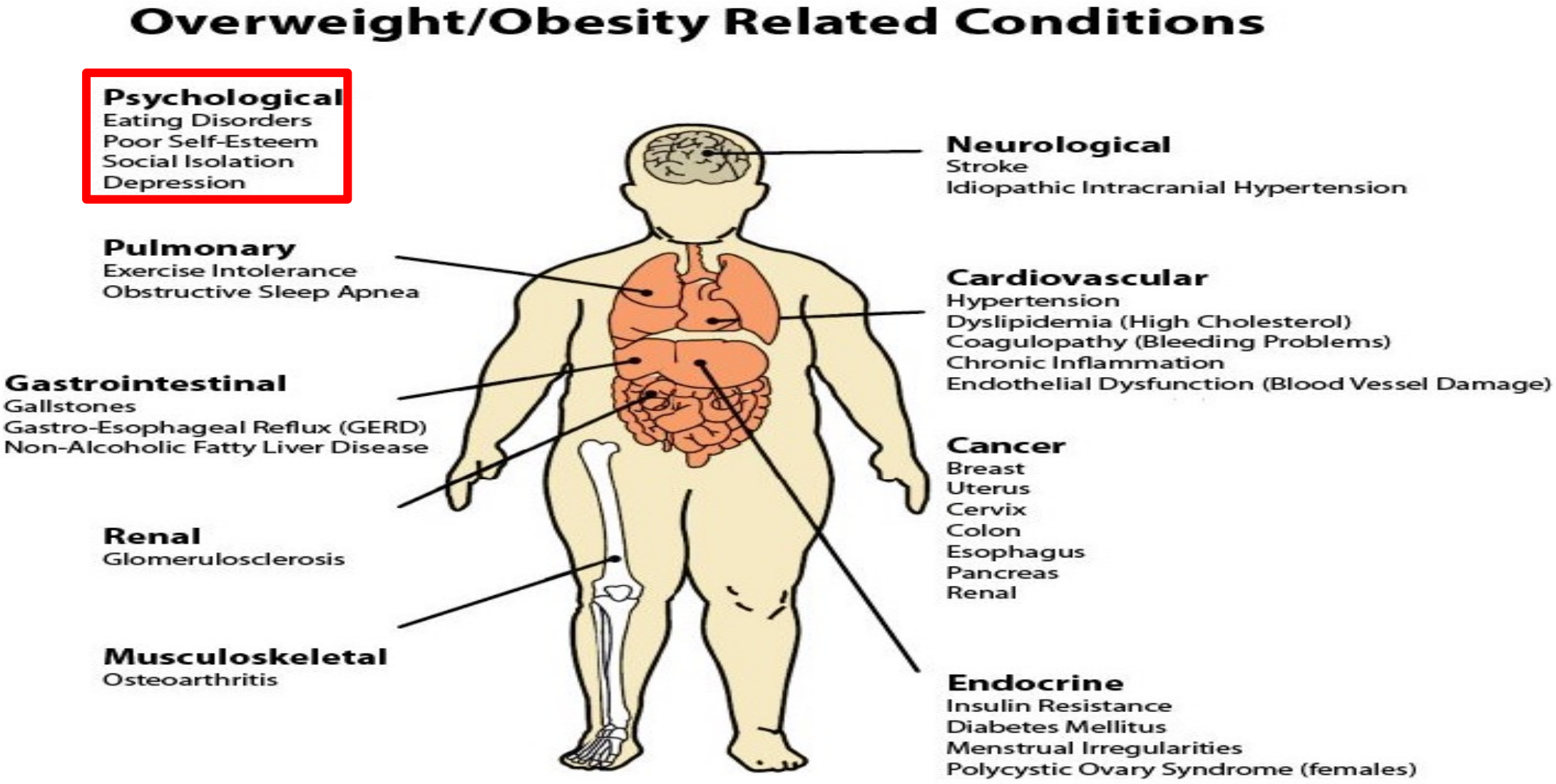
# 정신질환 동반한 비만환자 치료하기: 향정신성 제제 처방시 고려할 점

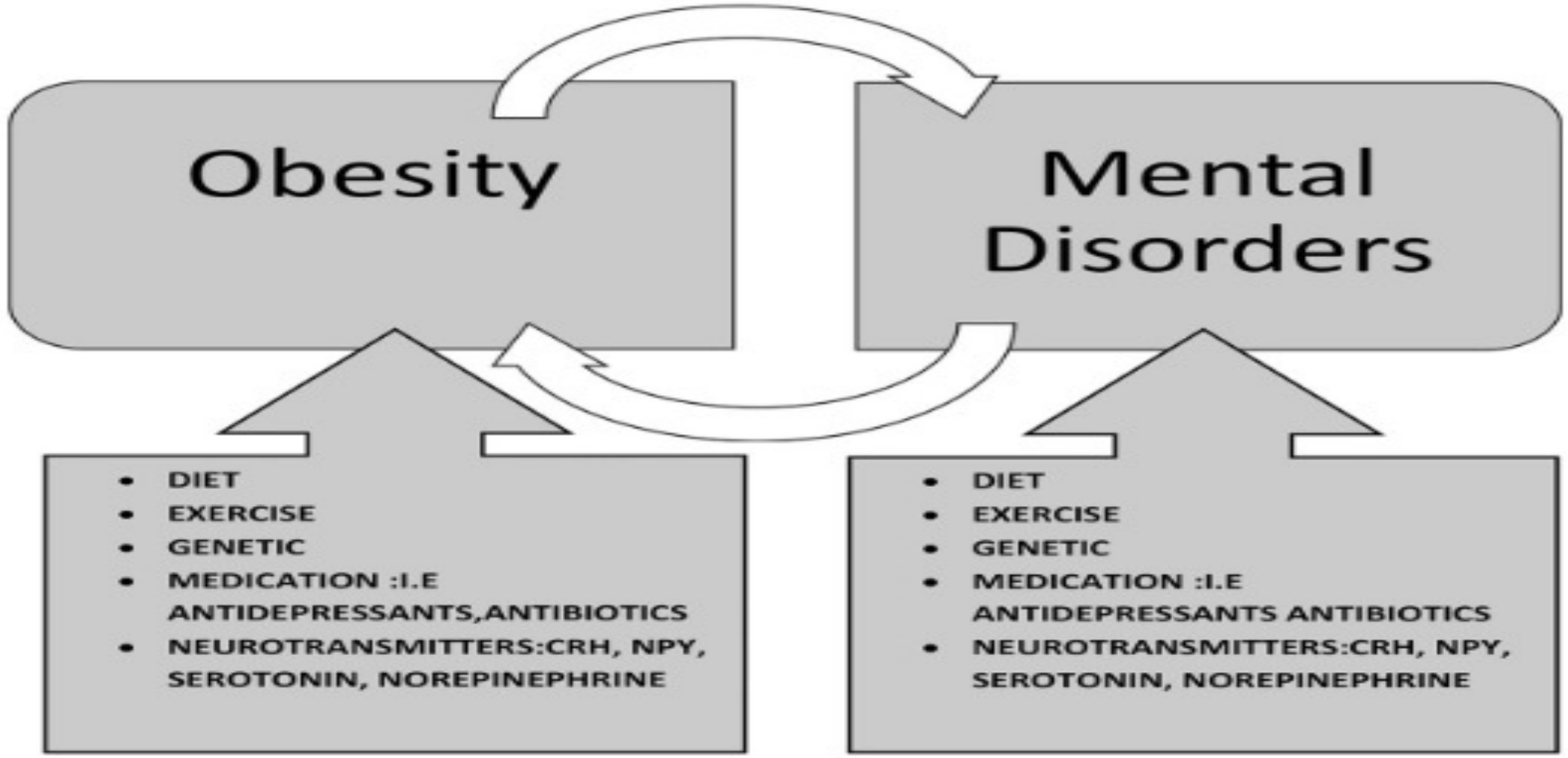
의정부 을지대병원

허연

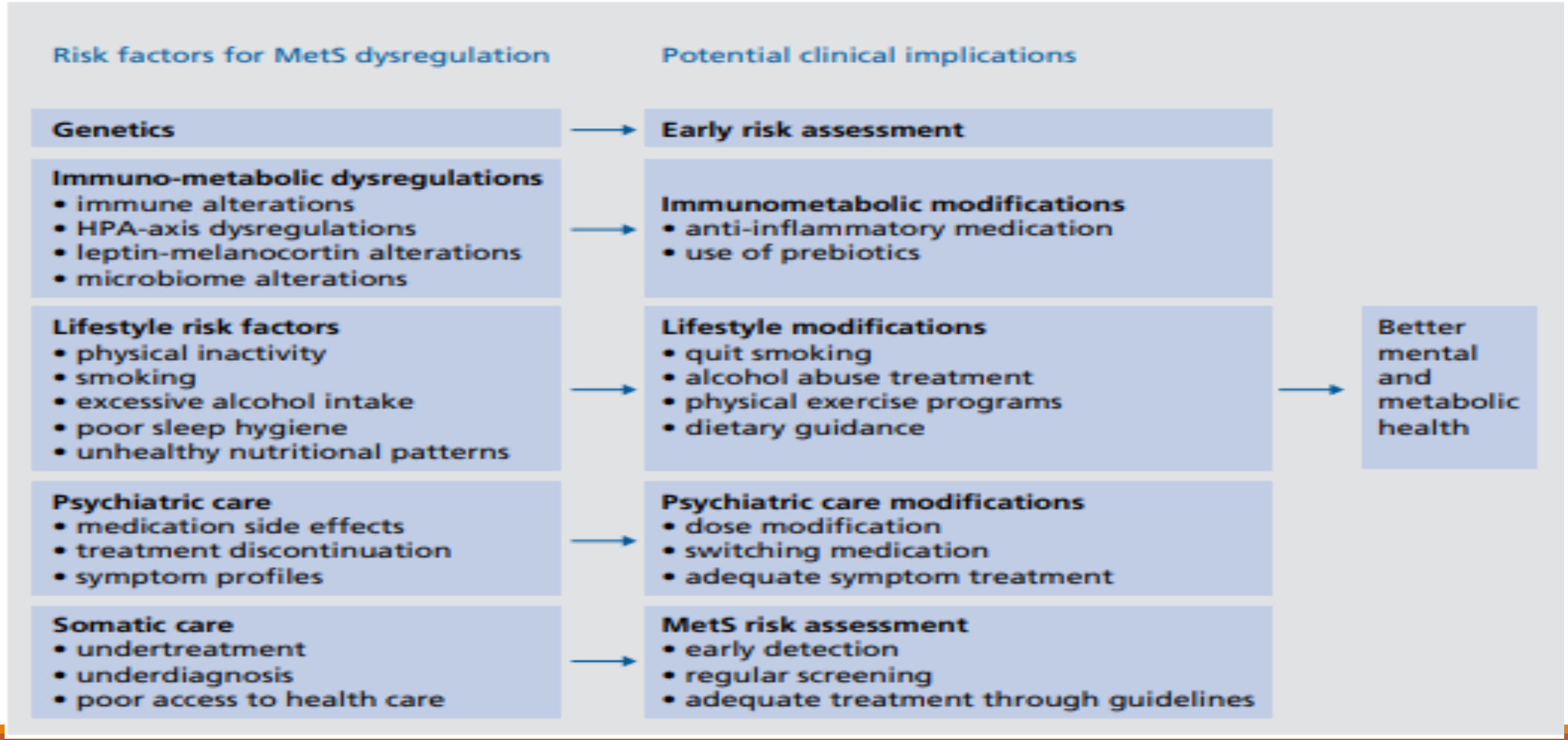
# The effects of obesity on the body



# Bidirectional interrelationship between obesity and mental disorders



# Risk factors in psychiatric patients



# Mental illness and obesity

- 13% of the world's population are obese.
- More that 300 million people worldwide have depression.
- 23% of obese individuals have comorbid depression.
- The prevalence of obesity among adults with severe mental health problems is as high as 55%.
- As independent risk factors, depression confers a 37% relative risk of obesity and obesity confers an 18% relative risk of depression; however, the excess risk of obesity in depression is small.

# Prevalence of selected mental disorders by BMI

**Table 2. Lifetime Prevalence of Selected Mental Disorders by BMI**

| Variable | Prevalence If BMI <30, % | Prevalence If BMI ≥30, % | OR (95% CI) |
|---|---|---|---|
| Lifetime | | | |
| Mood disorder | 18.3 | 22.0 | 1.27 (1.15-1.41) |
| Major depression | 16.0 | 18.6 | 1.21 (1.09-1.35) |
| Bipolar disorder | 1.9 | 2.8 | 1.47 (1.12-1.93) |
| Anxiety disorder | 9.8 | 12.3 | 1.28 (1.05-1.57) |
| Generalized anxiety | 5.4 | 6.5 | 1.20 (0.99-1.47) |
| Panic or agoraphobia | 5.6 | 7.1 | 1.27 (1.01-1.60) |
| Substance use disorder | 15.6 | 12.8 | 0.78 (0.65-0.93) |
| Last 12 months | | | |
| Mood disorder | 8.1 | 9.5 | 1.19 (1.00-1.42) |
| Major depression | 6.6 | 7.2 | 1.09 (0.89-1.34) |
| Bipolar disorder | 1.3 | 2.0 | 1.61 (1.07-2.43) |
| Anxiety disorder | 5.3 | 7.0 | 1.34 (1.07-1.66) |
| Generalized anxiety | 2.6 | 2.9 | 1.12 (0.77-1.64) |
| Panic or agoraphobia | 3.1 | 4.6 | 1.50 (1.20-1.87) |
| Substance use disorder | 4.3 | 2.9 | 0.65 (0.40-1.06) |

# Antipsychotic-induced weight gain

# Antipsychotics

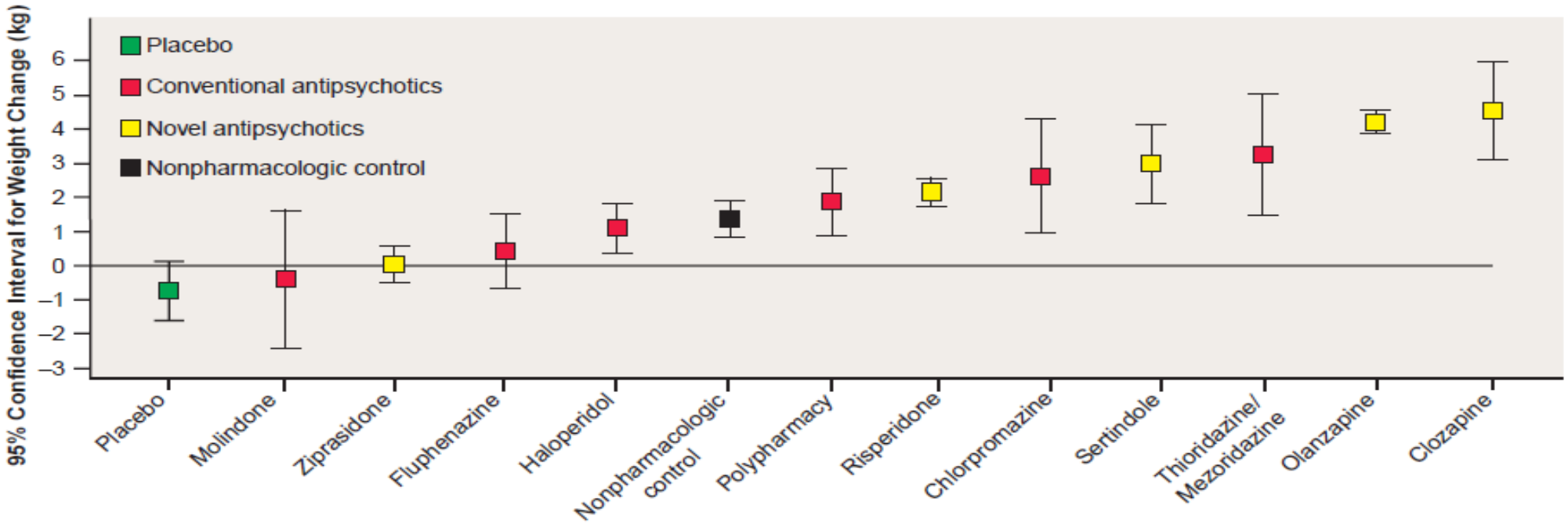
| Drug | Reference | Follow-up | n | Dose | Mean Weight Change | *P* Value |
|---|---|---|---|---|---|---|
| Adult population | | | | | | |
| Chlorpromazine, Perphenazine, Trifluoperazine, and Sulpride | Yoon[19] | 1 y | 111 | 275 mg/d of ce | +6.6 kg (SD 8.5) | <.001 |
| Olanzapine, Aripiprazole, Risperidone, and Quetiapine | Arterburn et al[37] | 8 y | 4962 | Not reported | <7% | Not reported |
| Aripiprazole | Nguyen et al[13] | 4 y | 1915 | Not reported | +2.97% (SE 0.28) over 180 d | <.001 |
| Amisulpiride, Quetiapine, Risperidone, and Ziprasidone | Tschoner et al[42] | 6 wk | 28 | Dose according to standard dosage procedures | +0.47 kg[b] | n.s. |
| Risperidone | Saddichha et al[41] | 6 wk | 99 | 4.4 ± 1.2 mg/d | >7% | <.001 |
| | Iqbal et al[39] | 1 y | 124 | 2 mg/d | −1.2 kg[b] | Not reported |
| | Tadger and Melamed[20] | 1 y | 100 | Not reported | +2.7 kg[b] | <.01 |
| | Yoon[19] | 1 y | 111 | 1-5 mg/d | +9.7 kg (SD 9.3) | <.001 |
| Olanzapine | Iqbal et al[39] | 1 y | 124 | 10 mg/d | +18.1 kg[b] | <.001 |
| | Tadger and Melamed[20] | 1 y | 100 | Not reported | +2.7 kg[b] | <.05 |
| | Yoon[19] | 1 y | 111 | 5-30 mg/d | +9.7 kg (SD 9.3) | <.001 |
| | Saddichha et al[41] | 6 wk | 99 | 16.5 ± 4.6 mg/d | >7% | <.001 |
| | Tschoner et al[42] | 6 wk | 28 | Dose according to standard dosage procedures | +2.59 kg[b] | <.01 |
| Quetiapine | Iqbal et al[39] | 1 y | 124 | 200 mg/d | +17.2 kg[b] | <.001 |
| Haloperidol | Saddichha et al[41] | 6 wk | 99 | 13.4 ± 3.6 mg/d | >7% | <.001 |
| | Iqbal et al[39] | 1 y | 124 | 10 mg/d | +7.9 kg[b] | <.001 |
| | Yoon[19] | 1 y | 111 | 275 mg/d of ce | +6.6 kg (SD 8.5) | <.001 |
| Trifluoperazine | Iqbal et al[39] | 1 y | 124 | 2 mg/d | +13.7 kg[b] | <.001 |

Obesity reviews. 2019;20:1680-1690

# First meta-analysis

Among newer antipsychotic agents, mean increases were as follows: clozapine, 4.45 kg; olanzapine, 4.15 kg; sertindole, 2.92 kg; risperidone, 2.10 kg; and ziprasidone, 0.04 kg.
Insufficient data were available to evaluate quetiapine at 10 weeks.

**FIGURE 1. 95% Confidence Intervals for Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random Effects Model**



# CATIE (The Clinical Antipsychotic Trials of Intervention Effectiveness) study

Weight gains of 7% or more were documented in 30%, 16%, 14%, and 7% of chronic schizophrenia patients treated with olanzapine, quetiapine, risperidone, and ziprasidone over an 18-month period.

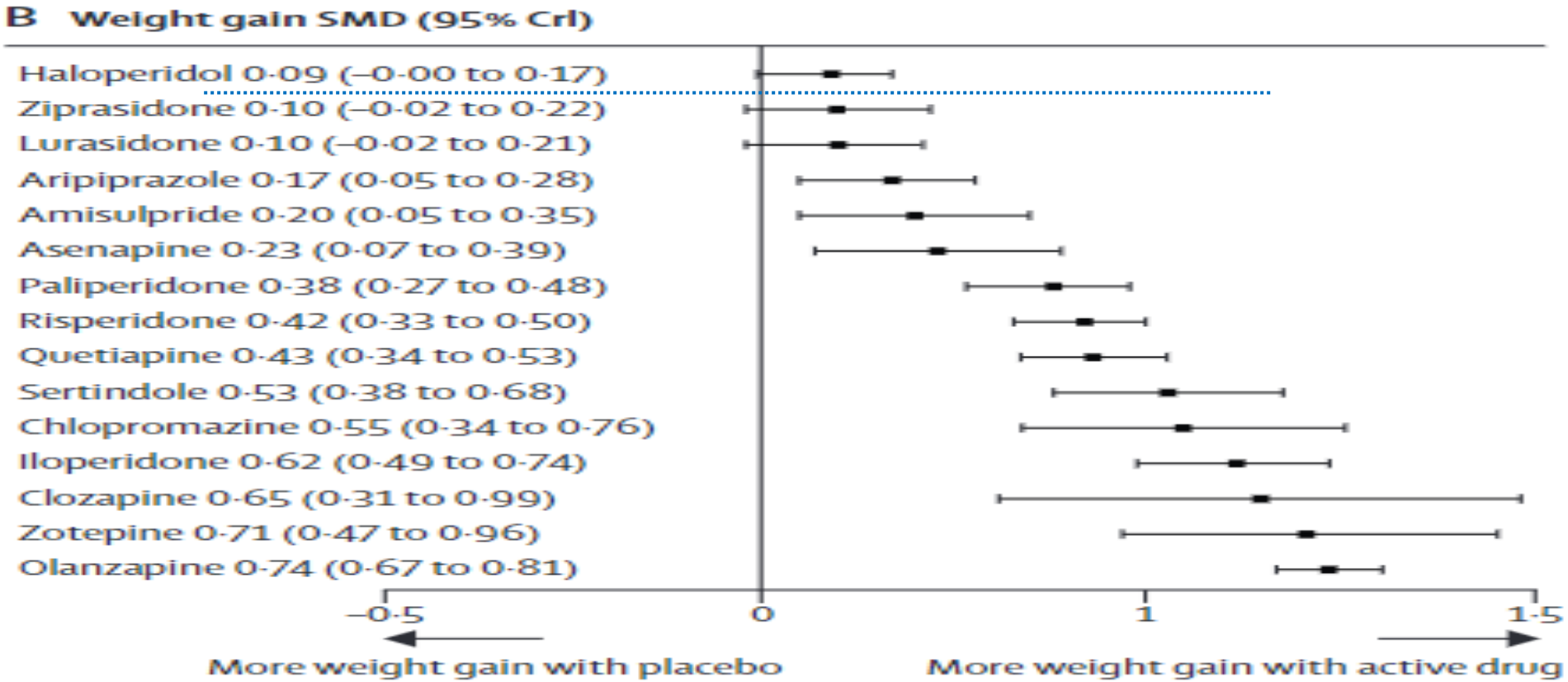
**Table 3. Outcome Measures of Safety among Randomized Patients.**

| Outcome | Olanzapine (N=336) | Quetiapine (N=337) | Risperidone (N=341) | Perphenazine (N=261)* | Ziprasidone (N=185) | P Value† |
|---|---|---|---|---|---|---|
| **Weight change from baseline to last observation¶** | | | | | | |
| Weight gain >7% — no./total no. (%) | 92/307 (30) | 49/305 (16) | 42/300 (14) | 29/243 (12) | 12/161 (7) | <0.001 |
| Weight change — lb | | | | | | |
| Mean ±SE | 9.4±0.9 | 1.1±0.9 | 0.8±0.9 | −2.0±1.1 | −1.6±1.1 | <0.001 |
| Median | 7 | 1 | 0 | −1 | −2 | |
| Range | −14 to 42 | −25 to 25 | −24 to 24 | −29 to 22 | −24 to 18 | |
| Weight change — lb/mo of treatment | | | | | | |
| Mean ±SE | 2.0±0.3 | 0.5±0.2 | 0.4±0.3 | −0.2±0.2 | −0.3±0.3 | <0.001 |
| Median | 0.8 | 0.1 | 0.0 | −0.1 | −0.3 | |
| Range | −1.4 to 9.5 | −4.4 to 6.3 | −4.6 to 5.7 | −4.9 to 4.0 | −5.3 to 5.9 | |
| **Discontinuation of treatment owing to intolerability — no. %** | | | | | | |
| Discontinuation | 62 (18) | 49 (15) | 34 (10) | 40 (15) | 28 (15) | 0.04 |
| Weight gain or metabolic effects | 31 (9) | 12 (4) | 6 (2) | 3 (1) | 6 (3) | <0.001 |

N Engl J Med 2005;353:1209-23

# A multiple-treatments meta-analysis to compare 15 antipsychotic drugs for schizophrenia

Standardised mean differences compared with placebo for weight gain varied from –0·09 for the best drug (haloperidol) to –0·74 for the worst drug (olanzapine)



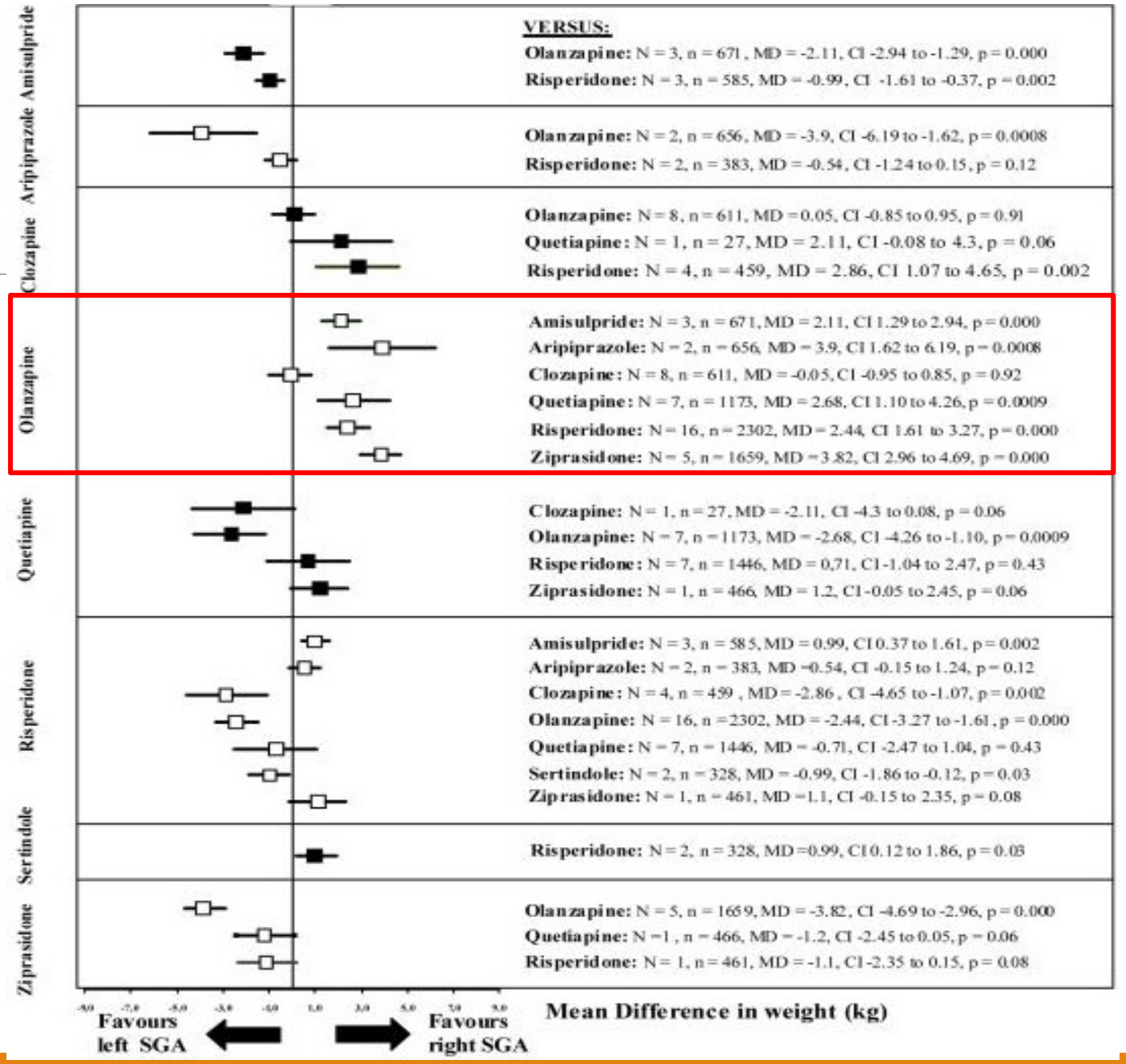
# Head-to head meta-analysis

- Highest amount of weight gain
  : Olanzapine and Clozapine

- Intermediate amounts of weight gain : Quetiapine, Risperidone and Sertindole

- Intermediate to low level of weight gain : Aripiprazole and Amisulpiride

- the least amount of weight gain
  : Ziprasidone




Schizophr Res. 2010 November ; 123(2-3): 225–233

# Meta analysis of the 307 included studies

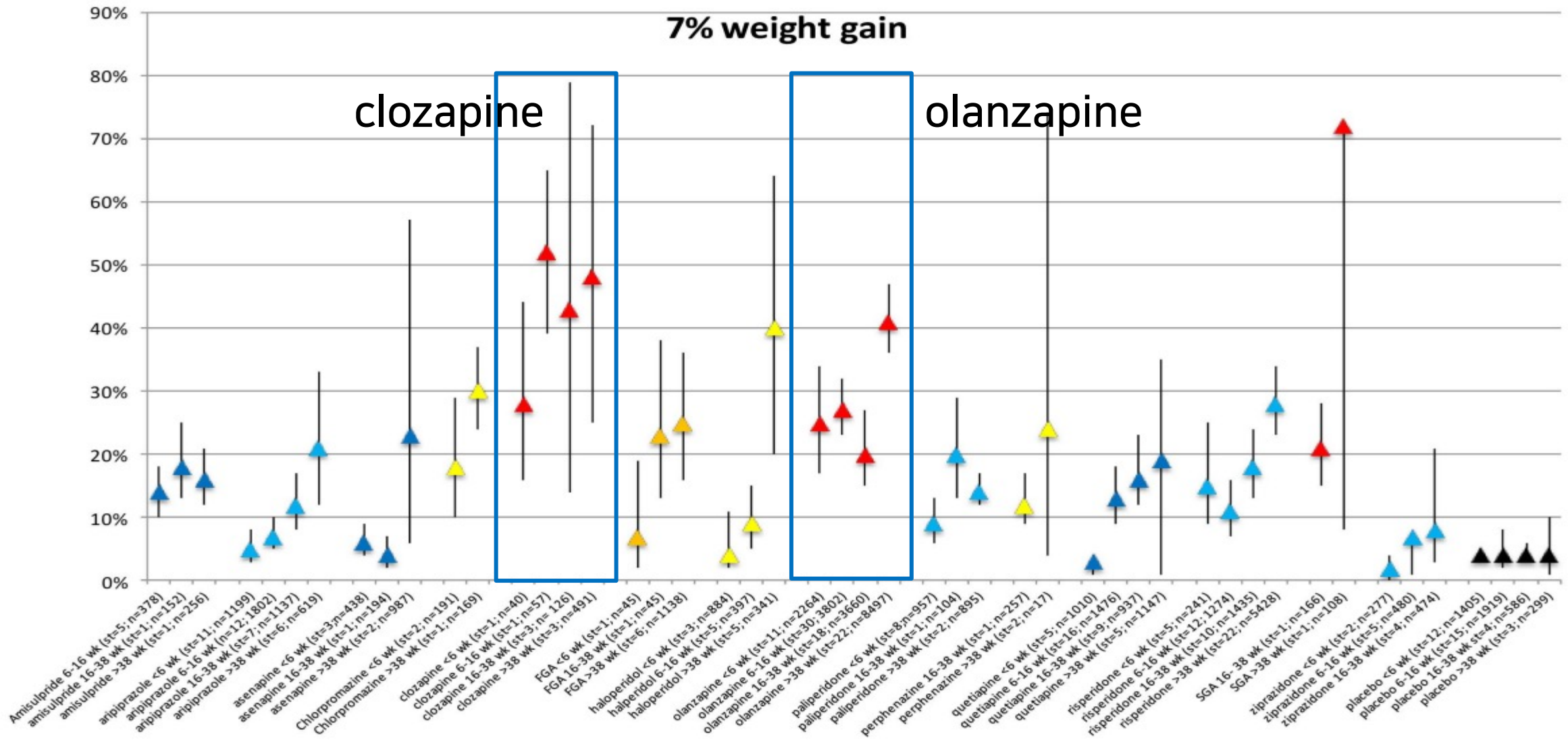
the crude data suggest that olanzapine show the most severe weight gain post-baseline, while FGA, for example haloperidol, are also associated with significant weight gain.

**Table 1.** Metaregression of weight changes per period.

| Period | aripiprazole | asenapine | clozapine | FGA | haloperidol | olanzapine | quetiapine | risperidone | ziprasidone | placebo |
|---|---|---|---|---|---|---|---|---|---|---|
| ≤6 wk* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6–16 wk | −0.46 *−1.78–0.85* | | −2.37 *−6.93–2.19* | −2.19 *−6.63–2.25* | −0.25 *−2.50–1.99* | 0.472 *−0.16–1.60* | 0.05 *−1.26–1.36* | −0.58 *−1.57–0.72* | −0.97 *−3.08–1.13* | 0.25 *−0.14–0.64* |
| 16–38 wk | **−1.43** ***−2.75–−0.12*** | −1.25 *−5.98–3.48* | −3.81 *−8.18–0.55* | | 2.75 *−0.58–6.08* | 0.26 *−0.68–1.20* | −0.54 *−1.94–0.86* | −0,03 −1.03–0.96 | −1.68 *−3.78–0.41* | −0.26 *−0.81–0.28* |
| >38 wk | −0.20 *−1.64–1.24* | 0.74 *−3.24–4.72* | 1.09 *−3.47–5.66* | 2.79 *−1.12–6.70* | 1.81 *−0.53–4.15* | **1.74** ***0.50–2.99*** | −0.85 *−2.56–0.87* | 0.37 −0.63–1.38 | −0.50 *−3.67–2.68* | **−1.08** ***−1.88–−0.29*** |

PLos One 2014 Apr 24;9(4):e94112.

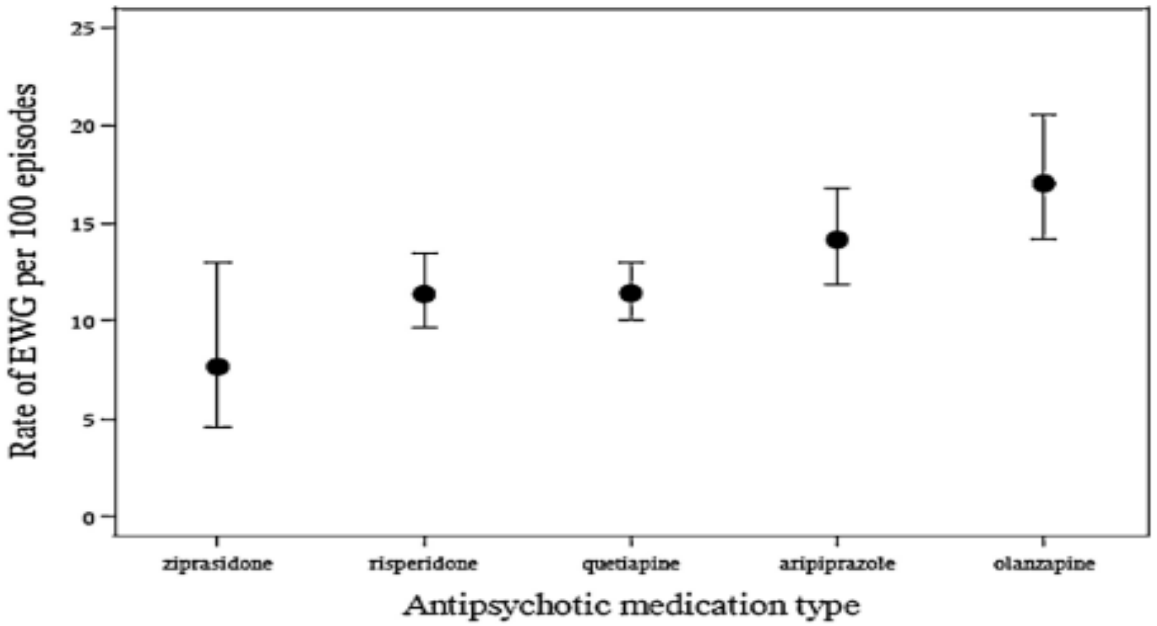
# Meta analysis of the 307 included studies

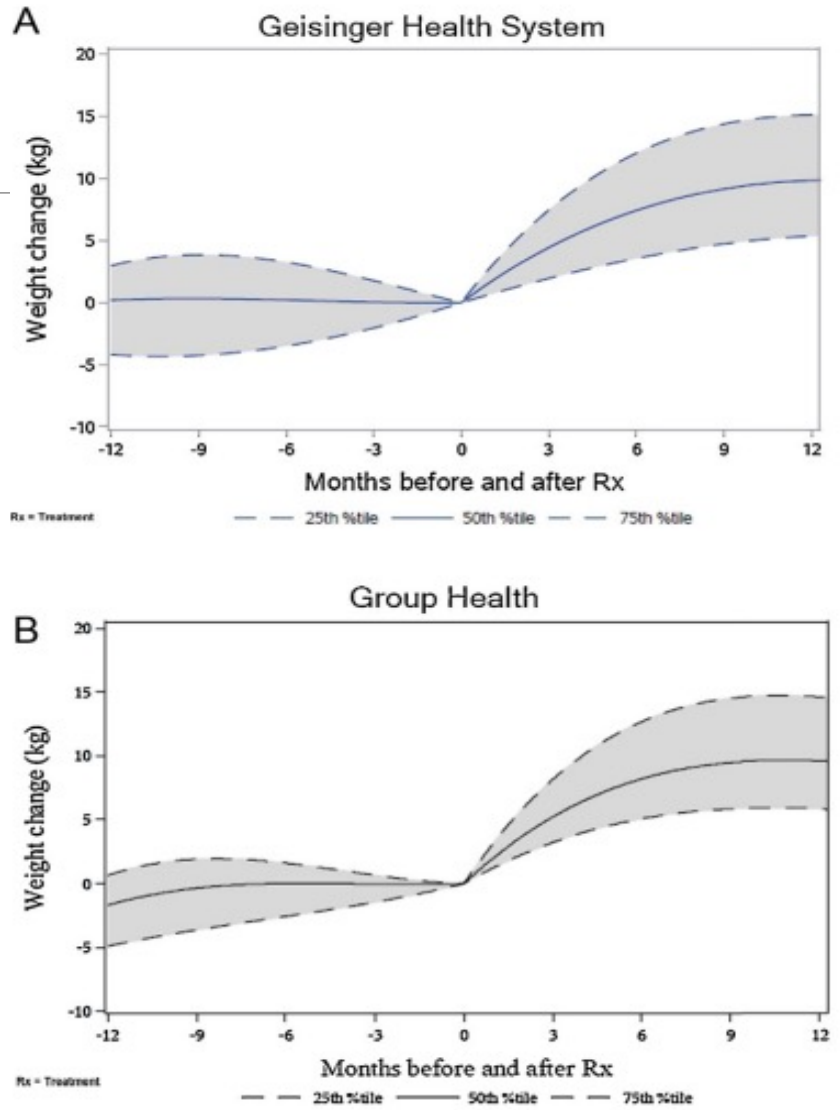



PLos One 2014 Apr 24;9(4):e94112.

# According to Arterburn et al

Weight gain occurred in 7.7—17.0% of SGA users.
At one year, the average weight gain was nearly 10 kg among SGA users

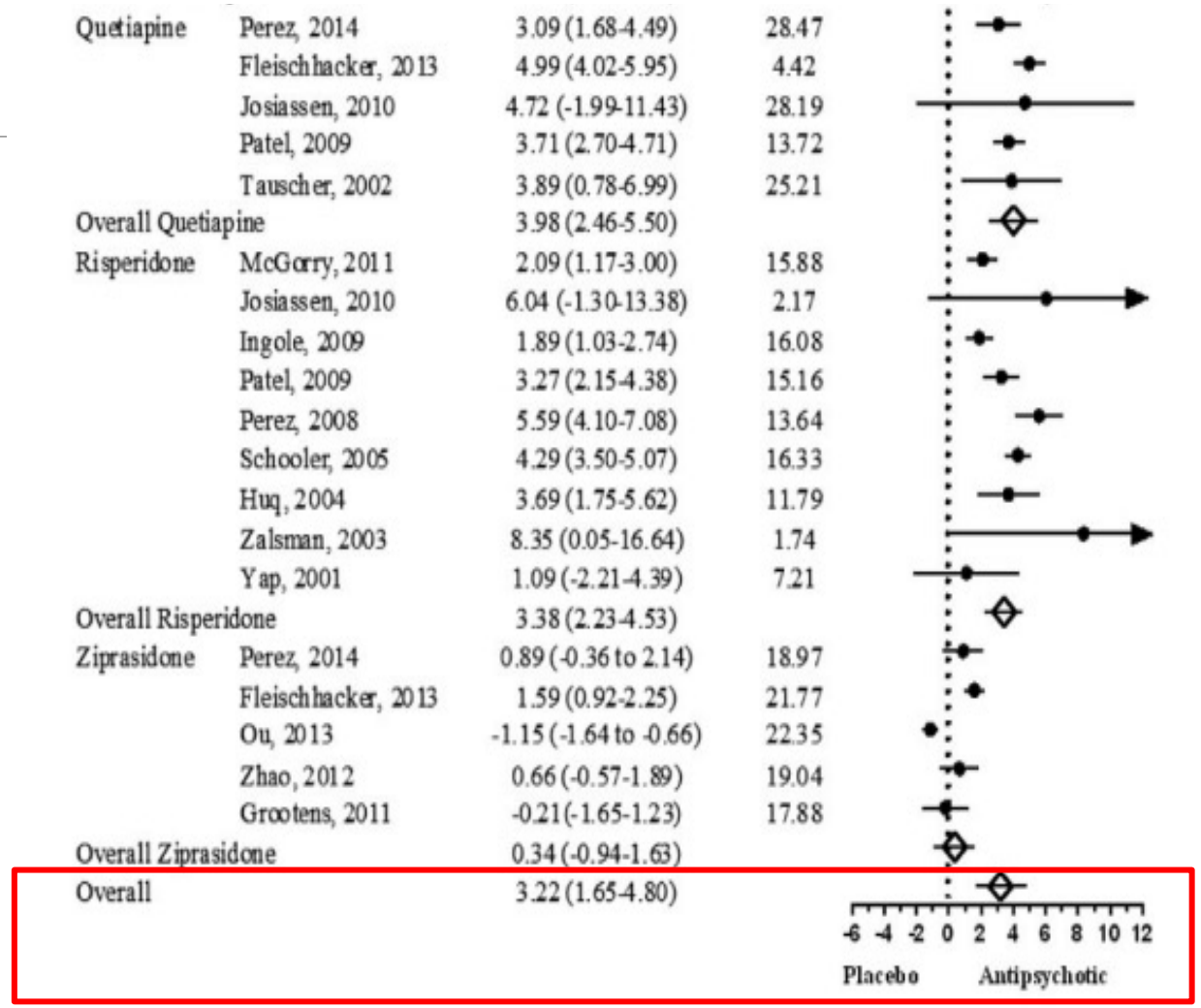



Obesity Research and clinical practice (2016) 10, 408-423

# A meta-analysis of Antipsychotic-induced weight change in the first-episode psychosis

Mean weight differences (kg) between placebo and antipsychotic medications in the short-term (≤12 weeks)

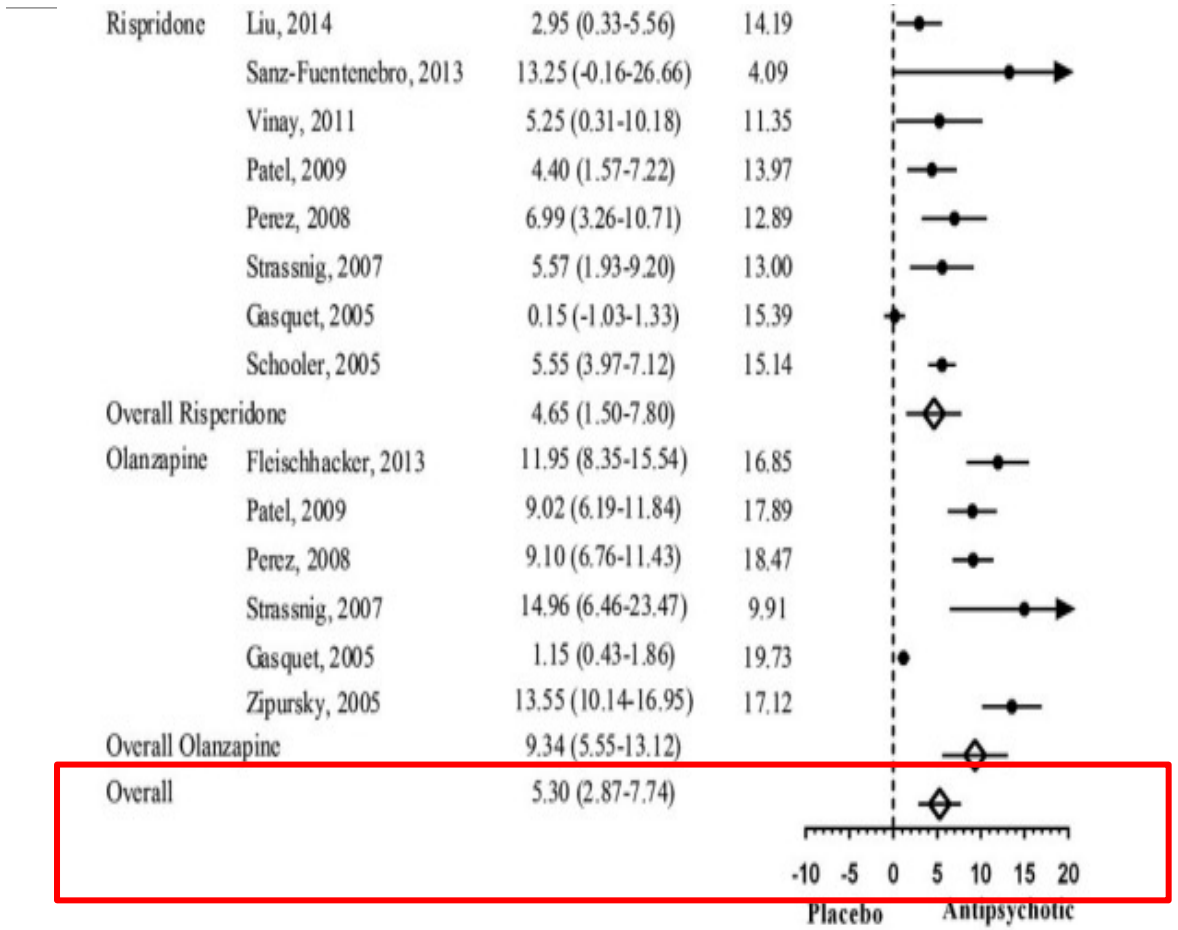



Early Intervention in Psychiatry 2016; 10: 193–202

# A meta-analysis of Antipsychotic-induced weight change in the first-episode psychosis

**Mean weight differences (kg) between placebo and antipsychotic medications in the long term (>12 weeks)**

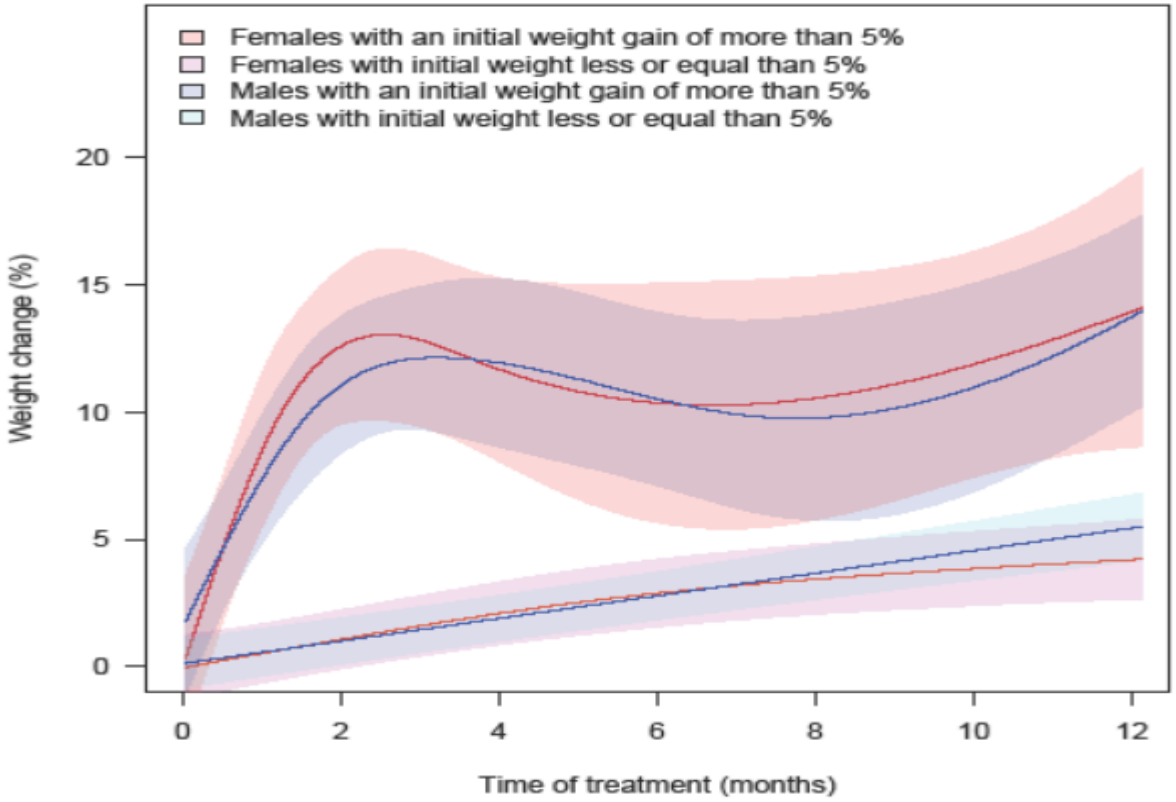
| Medication | Study name | Mean difference (CI) | Weight (%) |
|---|---|---|---|
| Amisulpride | Fleischhacker, 2013 | 7.75 (-1.46 to 12.96) | 100 |
| Blonanserin | Ninomiya, 2014 | 0.16 (-4.81 to 5.13) | 100 |
| Clorpromazine | Lieberman, 2003 | 6.55 (-2.32 to 15.42) | 100 |
| Ziprasidone | Fleischhacker, 2013 | 2.85 (-6.54 to 12.24) | 100 |
| Perfenazine | Strassnig, 2007 | -0.41 (-9.84 to 9.02) | 100 |
| Clozapine | Sanz-Fuentenebro, 2013 | 6.05 (-0.83 to 12.93) | 39.94 |
| | Lieberman, 2003 | 7.95 (5.23-10.66) | 60.05 |
| Overall Clozapine | | 7.19 (0.28-14.09) | |
| Haloperidol | Fleischhacker, 2013 | 5.35 (1.57-9.12) | 19.09 |
| | Perez, 2008 | 7.72 (4.11-11.32) | 19.37 |
| | Strassnig, 2007 | 2.13 (-1.45-5.71) | 19.40 |
| | Schooler, 2005 | 4.55 (2.99-6.10) | 22.13 |
| | Zipursky, 2005 | 5.15 (1.93-8.36) | 19.99 |
| Overall Haloperidol | | 4.96 (0.90-9.02) | |
| Quetiapine | Rasmussen, 2014 | 3.05 (-4.09 to 10.19) | 17.42 |
| | Liu, 2014 | 2.25 (-0.34 to 4.84) | 28.47 |
| | Fleischhacker, 2013 | 8.55 (4.77-12.32) | 25.70 |
| | Patel, 2009 | 3.53 (0.90-6.15) | 28.41 |
| Overall Quetiapine | | 4.37 (-0.08 to 8.83) | |
| Rispridone | Liu, 2014 | 2.95 (0.33-5.56) | 14.19 |
| | Sanz-Fuentenebro, 2013 | 13.25 (-0.16-26.66) | 4.09 |
| | Vinay, 2011 | 5.25 (0.31-10.18) | 11.35 |
| | Patel, 2009 | 4.40 (1.57-7.22) | 13.97 |
| | Perez, 2008 | 6.99 (3.26-10.71) | 12.89 |
| | Strassnig, 2007 | 5.57 (1.93-9.20) | 13.00 |
| | Gasquet, 2005 | 0.15 (-1.03-1.33) | 15.39 |
| | Schooler, 2005 | 5.55 (3.97-7.12) | 15.14 |
| Overall Risperidone | | 4.65 (1.50-7.80) | |
| Olanzapine | Fleischhacker, 2013 | 11.95 (8.35-15.54) | 16.85 |
| | Patel, 2009 | 9.02 (6.19-11.84) | 17.89 |
| | Perez, 2008 | 9.10 (6.76-11.43) | 18.47 |
| | Strassnig, 2007 | 14.96 (6.46-23.47) | 9.91 |
| | Gasquet, 2005 | 1.15 (0.43-1.86) | 19.73 |
| | Zipursky, 2005 | 13.55 (10.14-16.95) | 17.12 |
| Overall Olanzapine | | 9.34 (5.55-13.12) | |
| Overall | | 5.30 (2.87-7.74) | |




Early Intervention in Psychiatry 2016; 10: 193–202

# Time for weight gain

Patients with a weight gain >5% had a strong and fast increase of weight gain during the first three months of treatment




J Clin Psychiatry. 2015;76(11):e1417–e1423

# A ranks the antipsychotics according to the likelihood of causing weight gain, considering the current evidence

| 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] |

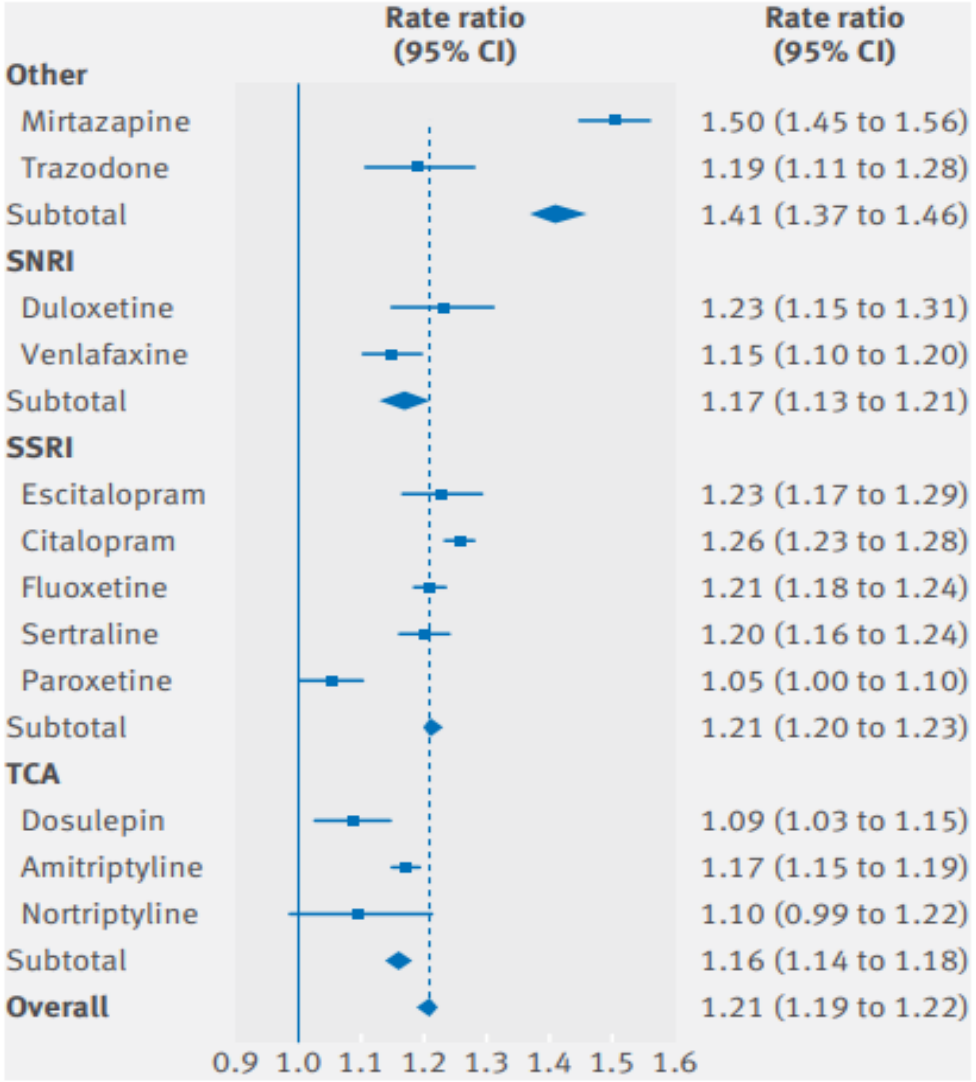
Neuropsychiatric Disease and Treatment 2017:13 2231–2241

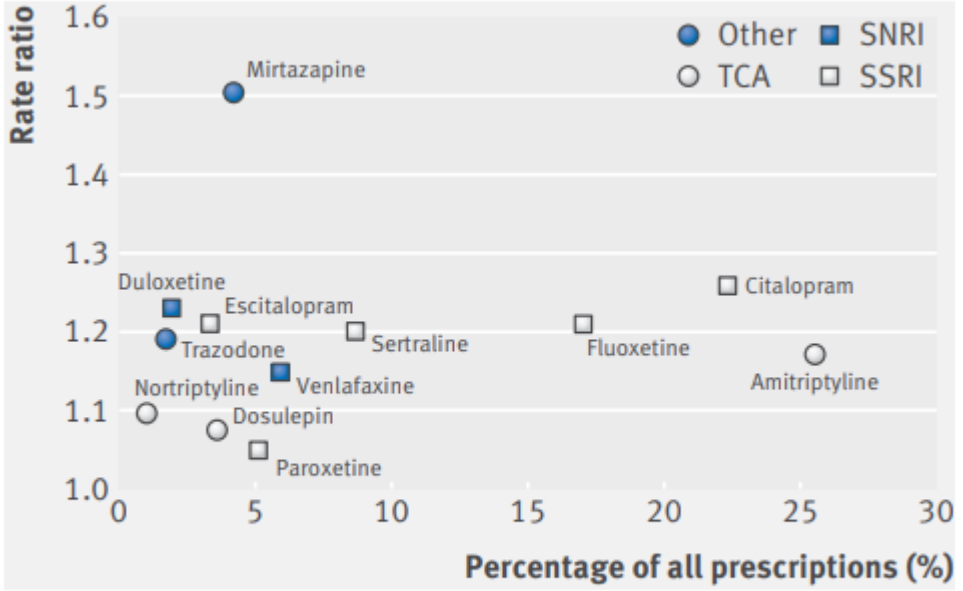
# Antidepressants

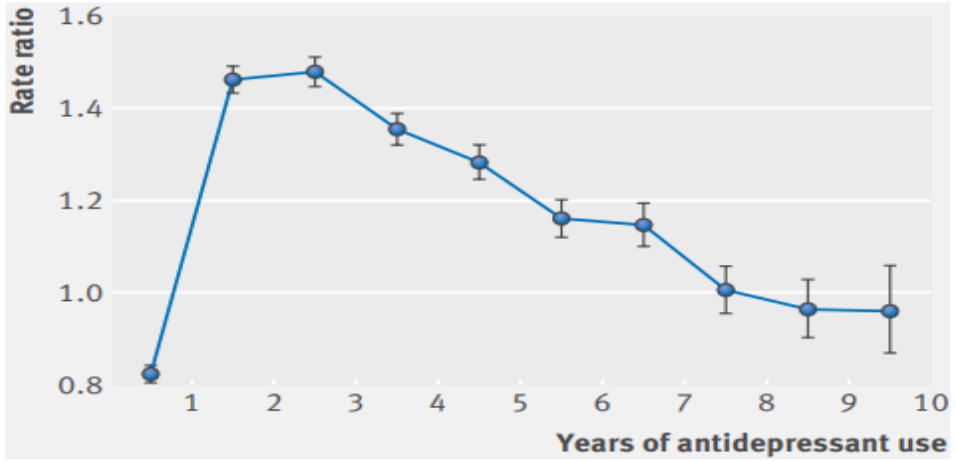
| Drug | Reference | Follow-up | n | Dose | Mean Weight Change | *P* Value |
|---|---|---|---|---|---|---|
| Adult population | | | | | | |
| Any antidepressant used | Patten et al[28] | 12 y | 14 117 | Not reported | +5.0 kg (95% CI, 4.3-5.8) | .01 |
| SSRIs | Shi et al[24] | 4.4 y | 2334 | Not reported | +0.61 kg/y (SD 1.89) | <.001 |
| | Kivimäki et al[26] | 4.8 y | 9197 | 200-400 daily doses | +2.8 kg[b] | Not reported |
| | Noordam et al[27] | 18 y | 7269 | 1.03 daily doses[a] | +4.2 kg[b] (in ≥90 d of treatment) | .005 |
| TCAs | Shi et al[24] | 4.4 y | 2334 | Not reported | −0.01 kg/y (SD 1.32) | .908 |
| | Kivimäki et a[26] | 4.8 y | 9197 | 200-400 daily doses | +2.7 kg[b] | Not reported |
| | Noordam et al[27] | 18 y | 7269 | 0.52 daily doses[a] | +2.9 kg[b] (in ≥90 d of treatment) | .68 |
| Escitalopram, Citalopram, Fluoxetine, Sertraline, Paroxetine, Dosulepin, Amitriptyline, Nortriptyline, Duloxetine, Venlafaxine, Mirtazapine, and Trazadone | Gafoor et al[10] | 10 y | 314 449 | Not reported | >5% | <.001 |
| Citalopram | Arterburn et al[25] | 2 y | 5932 | Not reported | +0.54 kg[b] | .4 |
| Paroxetine | Arterburn et a[25] | 2 y | 5932 | Not reported | +0.36 kg[b] | .78 |
| Sertraline | Arterburn et al[25] | 2 y | 5932 | Not reported | +2.7 kg[b] | .02 |
| Trazadone | Arterburn et al[25] | 2 y | 5932 | Not reported | +0.36 kg[b] | .75 |
| Duloxetine | Arterburn et al[25] | 2 y | 5932 | Not reported | −0.45 kg[b] | .88 |
| Mirtazapine | Arterburn et al[25] | 2 y | 5932 | Not reported | +5.3 kg[b] | .12 |
| Venlafaxine | Arterburn et al[25] | 2 y | 5932 | Not reported | −0.9 kg[b] | .67 |
| Bupropion | Arterburn et al[25] | 2 y | 5932 | Not reported | Non-smokers: −3.22 kg[b]<br>Smokers: +0.99 kg[b] | Non-smokers: <.01<br>Smokers: .33 |

**Obesity reviews. 2019;20:1680-1690**

# Antidepressant utilisation and incidence of weight gain during 10 years' follow-up



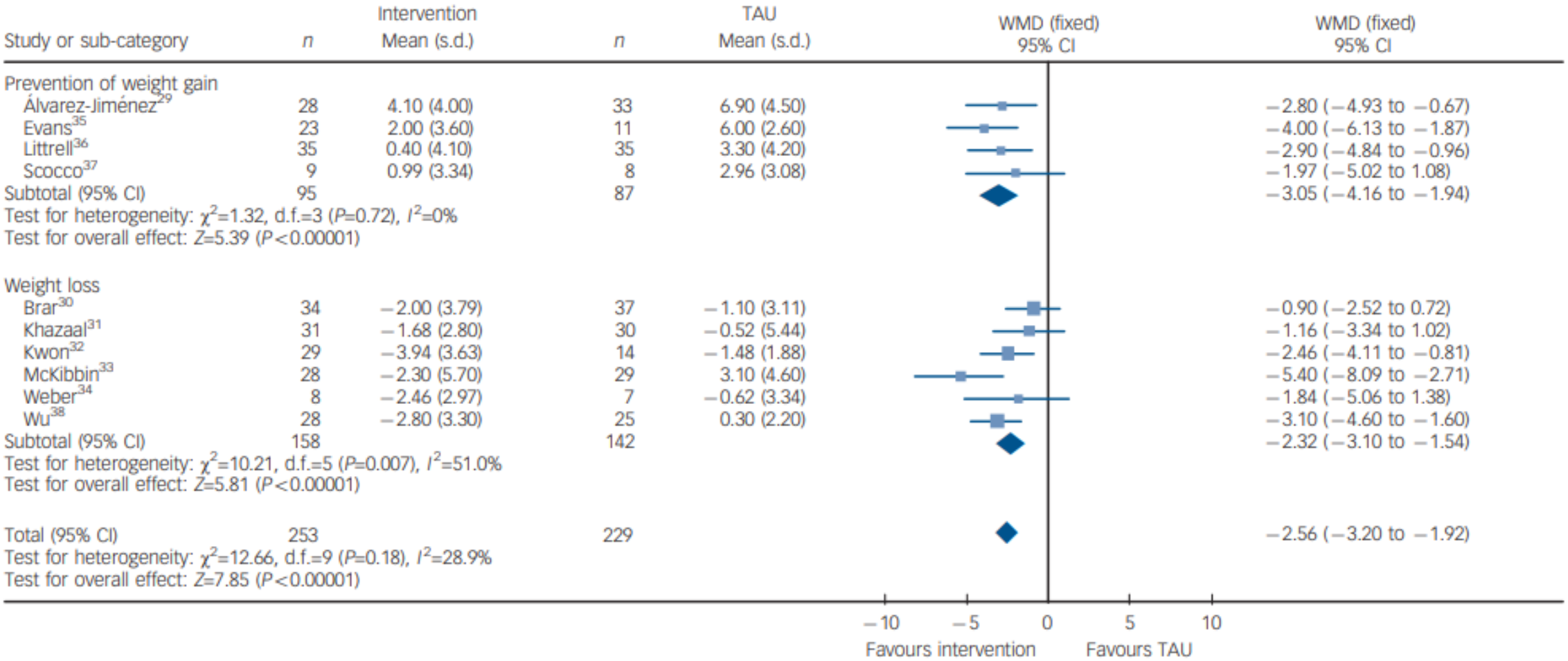




BMJ 2018;361:k1951

# Management of antipsychotic-induced weight gain

# Non-pharmacological

Individual or group interventions, or cognitive–behavioural therapy as well as nutritional counselling were effective



| Study or sub-category | Intervention n | Intervention Mean (s.d.) | TAU n | TAU Mean (s.d.) | WMD (fixed) 95% CI |
|---|---|---|---|---|---|
| Prevention of weight gain | | | | | |
| Álvarez-Jiménez[29] | 28 | 4.10 (4.00) | 33 | 6.90 (4.50) | −2.80 (−4.93 to −0.67) |
| Evans[35] | 23 | 2.00 (3.60) | 11 | 6.00 (2.60) | −4.00 (−6.13 to −1.87) |
| Littrell[36] | 35 | 0.40 (4.10) | 35 | 3.30 (4.20) | −2.90 (−4.84 to −0.96) |
| Scocco[37] | 9 | 0.99 (3.34) | 8 | 2.96 (3.08) | −1.97 (−5.02 to 1.08) |
| Subtotal (95% CI) | 95 | | 87 | | −3.05 (−4.16 to −1.94) |
| Test for heterogeneity: $\chi^2$=1.32, d.f.=3 ($P$=0.72), $I^2$=0% | | | | | |
| Test for overall effect: $Z$=5.39 ($P$<0.00001) | | | | | |
| Weight loss | | | | | |
| Brar[30] | 34 | −2.00 (3.79) | 37 | −1.10 (3.11) | −0.90 (−2.52 to 0.72) |
| Khazaal[31] | 31 | −1.68 (2.80) | 30 | −0.52 (5.44) | −1.16 (−3.34 to 1.02) |
| Kwon[32] | 29 | −3.94 (3.63) | 14 | −1.48 (1.88) | −2.46 (−4.11 to −0.81) |
| McKibbin[33] | 28 | −2.30 (5.70) | 29 | 3.10 (4.60) | −5.40 (−8.09 to −2.71) |
| Weber[34] | 8 | −2.46 (2.97) | 7 | −0.62 (3.34) | −1.84 (−5.06 to 1.38) |
| Wu[38] | 28 | −2.80 (3.30) | 25 | 0.30 (2.20) | −3.10 (−4.60 to −1.60) |
| Subtotal (95% CI) | 158 | | 142 | | −2.32 (−3.10 to −1.54) |
| Test for heterogeneity: $\chi^2$=10.21, d.f.=5 ($P$=0.007), $I^2$=51.0% | | | | | |
| Test for overall effect: $Z$=5.81 ($P$<0.00001) | | | | | |
| Total (95% CI) | 253 | | 229 | | −2.56 (−3.20 to −1.92) |
| Test for heterogeneity: $\chi^2$=12.66, d.f.=9 ($P$=0.18), $I^2$=28.9% | | | | | |
| Test for overall effect: $Z$=7.85 ($P$<0.00001) | | | | | |



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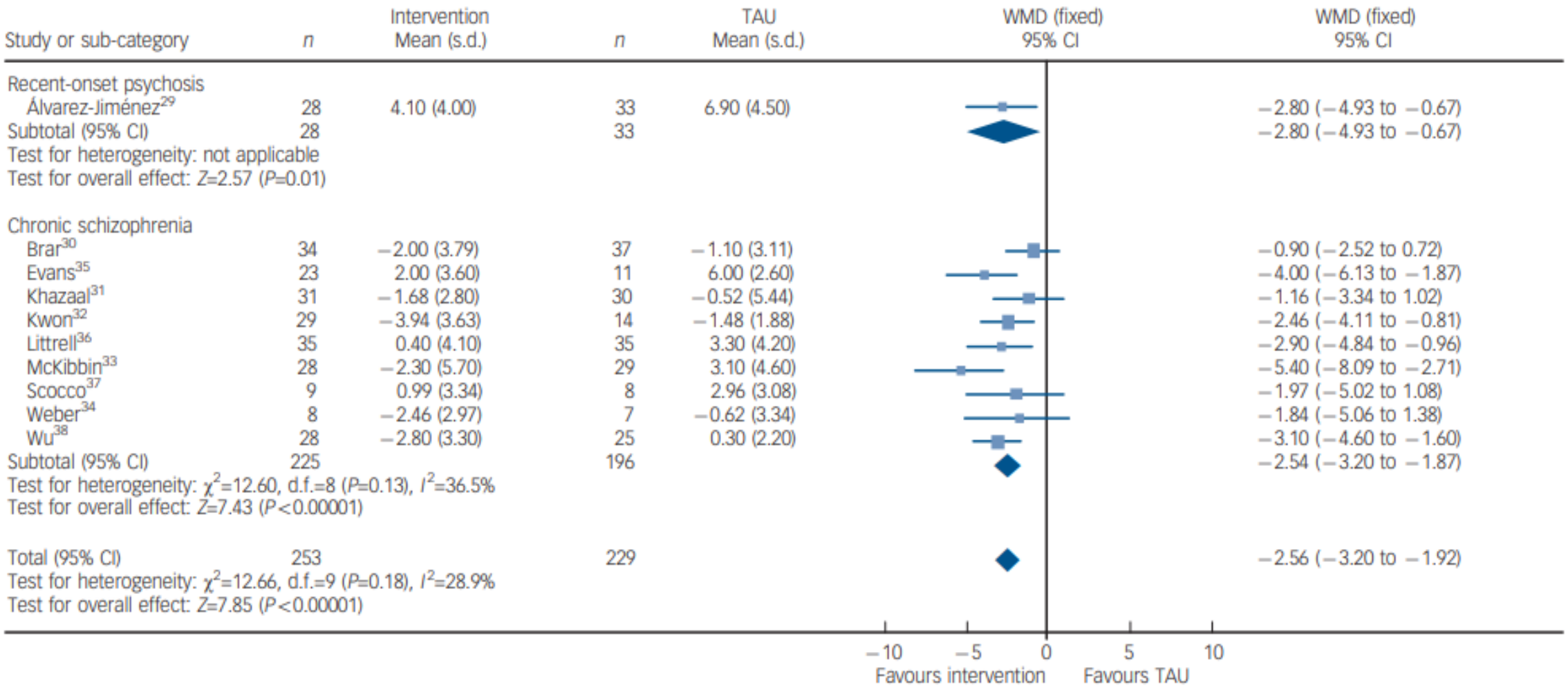
# Non-pharmacological

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# Pharmacological_adding

| Added Treatment | AAP | Study | Pharmacological Response |
|---|---|---|---|
| Metformin | Olanzapine | Double-blind study: 25 patients randomly assigned to olanzapine plus metformin or olanzapine plus placebo for 24 weeks. | Metformin-group gained 3% of body weight compared to 7% for placebo group. BMI change was 0.85 in metformin-group vs. 2.02 in placebo-group. |
| | | 40 patients randomly assigned treatment with olanzapine plus metformin or olanzapine plus placebo for 12 weeks. | Metformin-group vs. placebo group resulted in lower increase in body weight (1.90 vs. 6.87), fasting insulin level (0.81 vs. 6.78) and insulin resistance index (0.22 vs. 1.49). |
| | | 80 patients taking olanzapine were randomized metformin or placebo comedication treatment for 12 weeks. | Body weight change was −1.4 in metformin-group and non-significant in placebo. Insulin resistance increased after placebo and not after metformin. |
| | | 40 patients taking olanzapine were assigned to metformin or placebo for 14 weeks. | No significant improvements for treated vs. placebo group. |
| | Clozapine | 55 subjects taking clozapine for at least 3 months, were assigned to metformin or placebo for 24 weeks. | Body weight, BMI, fasting plasma glucose, HDL, insulin level had significant changes in the metformin-group. |
| | | 61 patients treated with clozapine were randomly assigned to metformin extended release or placebo for 14 weeks. | Mean change in body weight was −1.87 kg for metformin-group and 0.16 kg for placebo-group Insulin and the triglyceride/HDL ratio significantly decreased after metformin. |
| Rosiglitazione | Olanzapine | 12-week double blind study on 30 patients treated with olanzapine were allocated to rosiglitazione or placebo. | Insulin and the insulin resistance significantly decreased after rosiglitazone, while no effect was seen on weight gain and lipid profile. |
| | Clozapine | 8-week double blind, placebo-controlled trial of rosiglitazone 4 mg/day in 18 clozapine-treated schizophrenia subjects with insulin resistance. | Non-significant improvement on glucose utilization and insulin sensitivity index; significant reduction in LDL level in rosiglitazone group. |

# Pharmacological_adding

| Added Treatment | AAP | Study | Pharmacological Response |
|---|---|---|---|
| **Liraglutide** | **Olanzapine or clozapine** | 103 patients with a BMI > 27 and prediabetes randomly assigned to liraglutide or placebo for 16 weeks. | Liraglutide-group (63.8%) developed normal glucose tolerance compared with placebo-group (16%). Liraglutide induced a placebo-subtracted body weight loss of 5.3 kg. |
| **Exenatide** | **Clozapine** | 28 patients treated with clozapine randomly assigned to exenatide extended release or standard care for 24 weeks. | 6 people on exenatide achieved >5% weight loss vs. 1 usual care. Participants on exenatide had greater weight loss (−5.29 kg vs. −1.12 kg), BMI reduction (−1.78 vs. −0.39), reduced fasting glucose (−0.34 vs. 0.39) and HbA1c (−0.21 vs. 0.03) compared to control. |

# Psychiatric effects of anti-obesity medications

# Liraglutide – Warnings and precautions

- Suicidal behavior and ideation: In adult clinical trials, 9 (0.3%) of 3,384 patients treated with saxenda® and 2 (0.1%) of the 1,941 treated with placebo reported suicidal ideation; one of the saxenda® treated patients attempted suicide. In a pediatric trial, 1(0.8%) of the 125 saxenda® treated patients died by suicide. There was insufficient information to establish a causal relationship to saxenda®.
- Monitor patients for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
- Discontinue treatment if patients experience suicidal thoughts or behaviors.
- Avoid saxenda® in patients with a history of suicidal attempts or active suicidal ideation.

# Contrave ® – Common adverse reactions

| Adverse reaction | Contrave 32mg/360mg (N=2,545) | Placebo (N=1,515) |
|---|---|---|
| Insomnia | 9.2 | 5.9 |
| Anxiety | 4.2 | 2.8 |
| Irritability | 2.6 | 1.8 |

Clinical Research

# Psychiatric adverse events and effects on mood with prolonged-release naltrexone/bupropion combination therapy: a pooled analysis

Xavier Pi-Sunyer[1] · Caroline M. Apovian[2] · Susan L. McElroy[3] · Eduardo Dunayevich[4] · Lisette M. Acevedo[5] · Frank L. Greenway[6]

**Background/objectives** Prolonged-release (PR) naltrexone 32 mg/bupropion 360 mg (NB) is approved for chronic weight management as an adjunct to reduced-calorie diet and increased physical activity. Central nervous system-active medications have the potential to affect mood; therefore, post hoc analysis of clinical trial data was conducted to evaluate psychiatric adverse events (PAEs) and effects on mood of NB therapy versus placebo.

**Subjects/methods** Data were pooled from 5 prospective, double-blind, randomized, placebo-controlled clinical trials (duration range, 24–56 weeks) of NB in subjects with overweight or obesity. PAEs were collected via AE preferred terms, organized into major subtopics (e.g., anxiety, depression, sleep disorders), and divided into category terms (e.g., anxiety, potential anxiety symptoms). Additionally, the Inventory of Depressive Symptomatology Self Report (IDS-SR; score range 0–84) and the Columbia Classification Algorithm of Suicide Assessment (C-CASA) evaluated treatment-emergent depressive/anxiety symptoms and suicidal behavior/ideation, respectively.

**Table 3** Summary of depression, anxiety, and sleep disorder-related adverse events based on grouped preferred terms in subjects with ≥1 event

| Category[a] Preferred term, *n* (%) | NB (*n* = 2545) | Placebo (*n* = 1515) | NB vs placebo *P*-value |
|---|---|---|---|
| Anxiety | 138 (5.4) | 50 (3.3) | 0.029 |
| Anxiety | 108 (4.2) | 43 (2.8) | 0.118 |
| Nervousness | 13 (0.5) | 2 (0.1) | 0.071 |
| Tension | 10 (0.4) | 2 (0.1) | 0.374 |
| Panic attack | 6 (0.2) | 3 (0.2) | 0.912 |
| Fear | 2 (<0.1) | 0 | 0.319 |
| Panic reaction | 1 (<0.1) | 0 | 0.476 |
| Generalized anxiety disorder | 0 | 1 (<0.1) | 0.087 |
| Hyperventilation | 0 | 0 | |
| Depression | 47 (1.8) | 41 (2.7) | 0.014 |
| Depression | 24 (0.9) | 23 (1.5) | 0.088 |
| Depressed mood | 23 (0.9) | 18 (1.2) | 0.067 |
| Dysthymic disorder | 1 (<0.1) | 1 (<0.1) | 0.613 |
| Suicidal ideation | 1 (<0.1) | 3 (0.2) | 0.045 |
| Major depression | 0 | 1 (<0.1) | 0.087 |
| Sleep disorders | 322 (12.7) | 119 (7.9) | <0.001 |
| Insomnia | 233 (9.2) | 89 (5.9) | <0.001 |
| Sleep disorder | 34 (1.3) | 12 (0.8) | 0.311 |
| Abnormal dreams | 25 (1.0) | 6 (0.4) | 0.114 |
| Middle insomina | 16 (0.6) | 3 (0.2) | 0.095 |
| Poor quality sleep | 8 (0.3) | 2 (0.1) | 0.336 |
| Initial insomnia | 6 (0.2) | 4 (0.3) | 0.225 |
| Nightmare | 7 (0.3) | 1 (<0.1) | 0.615 |
| Sleep apnea syndrome | 5 (0.2) | 2 (0.1) | 0.594 |
| Terminal insomnia | 2 (<0.1) | 2 (0.1) | 0.604 |

32 mg naltrexone PR plus 360 mg bupropion PR (or 32 mg naltrexone immediate release plus 400 mg bupropion PR in study NB-201), *PR* prolonged release

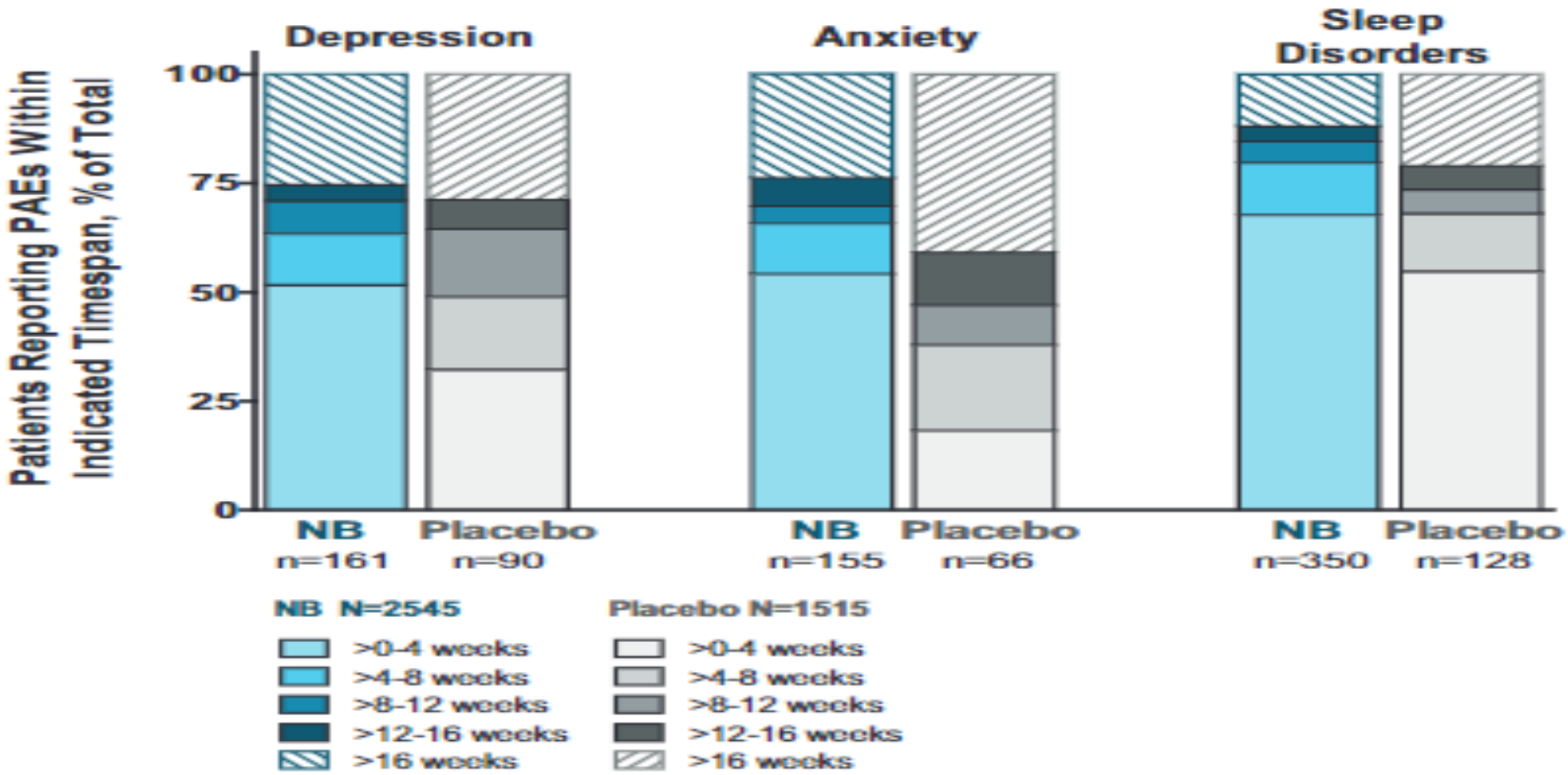


**Fig. 1** Participants reporting PAEs by treatment week for major subtopics of anxiety, depression, and sleep disorders. Data are presented as percent of participants reporting PAEs for each subtopic. The total number of NB or placebo patients reporting PAEs for each subtopic are listed below each bar. NB, 32 mg naltrexone PR plus 360 mg bupropion PR (or 32 mg naltrexone immediate release plus 400 mg bupropion PR in study NB-201); *PAE* psychiatric adverse event, *PR* prolonged release

# Qsymia – Adverse reactions

| | Placebo (N=1,561) | Qsymia 3.75/23mg (N=240) | Qsymia 7.5/46mg (N=240) | Qsymia 15/92mg (N=240) |
|---|---|---|---|---|
| Psychiatric disorders | | | | |
| Insomnia | 4.7 | 5.0 | 5.8 | 9.4 |
| Depression | 2.2 | 3.3 | 2.8 | 4.3 |
| Anxiety | 1.9 | 2.9 | 1.8 | 4.1 |

# Qsymia – Adverse reactions

- The proportion of patients in 1-year controlled trials of Qsymia reporting one or more adverse reactions related to mood and sleep disorders was 15.8%, 14.5%, and 20.6% with Qsymia 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg, respectively, compared to 10.3% with placebo.
- The majority of these events first occurred within the initial 12 weeks of drug therapy; however, in some patients, events were reported later in the course of treatments.

# Qsymia – Suicidal behavior and ideation

- Antiepileptic drugs (AEDs), including topiramate, a component of Qsymia, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication.
- Patients treated with Qsymia should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.