

CAN METFORMIN PREVENT Antipsychotic-Induced Weight Gain



PRESENTATION BY:

DR. HARVINDER SINGH





CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



DR. SATINDER PAL KAUR

FAMILY MEDICINE
OBESITY MEDICINE





CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



LEARNING OBJECTIVES:

- ✓ Should Metformin be Used for the Prevention of AIWG?
- ✓ What Predictors, Parameters & Thresholds Should Inform the Decision of When to Intervene?
- ✓ Does the Antipsychotic Class Matter in Decision-Making?
- ✓ What Dose of Metformin Should be Used for AIWG Prevention?
- ✓ What Monitoring is Recommended with Metformin Treatment?
- ✓ Understanding Metformin's Adverse Events
- ✓ When Should Metformin be AVOIDED & STOPPED?
- ✓ When are GLP-1 Agonists Indicated?



CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



SCHIZOPHRENIA BULLETIN

The Journal of Psychoses and Related Disorders

> [Schizophr Bull.](#) 2024 Dec 9:sbae205. doi: 10.1093/schbul/sbae205. Online ahead of print.

Metformin for the Prevention of Antipsychotic-Induced Weight Gain: Guideline Development and Consensus Validation

Aoife Carolan^{1 2}, Caroline Hynes-Ryan^{1 2}, Sri Mahavir Agarwal^{3 4 5 6}, Rita Bourke¹,
Walter Cullen⁷, Fiona Gaughran^{8 9}, Margaret K Hahn^{3 4 5 6 10 11}, Amir Krivoy^{12 13},
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Michael J Norton^{21 22}, Karen O'Connor^{23 24}, Benjamin I Perry^{25 26}, Toby Pillinger⁸,
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Affiliations + expand

PMID: 39657713 DOI: [10.1093/schbul/sbae205](#)



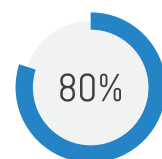
CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



Weight Gain in Serious Mental Illness:

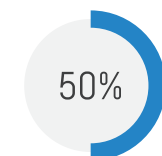


- Rapid & Nonlinear Trajectory



- ~80% experiencing significant weight gain ($\geq 7\%$ of baseline weight):
within a year of treatment for first-episode psychosis

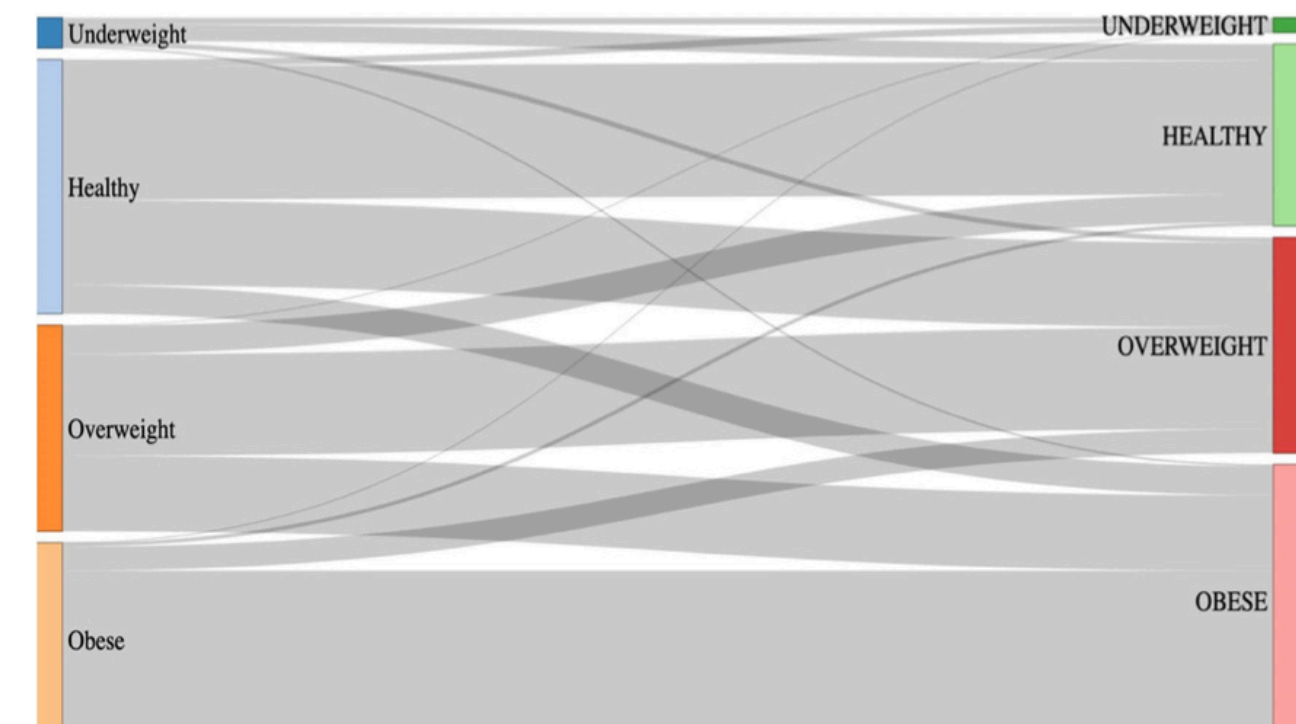
1
YEAR



- ~ 50% with healthy baseline weight:
overweight/obesity within 5 years of antipsychotic treatment

5
YEARS

UK longitudinal study
Ann Gen Psychiatry . 2024 Jan 3;23(1):1.





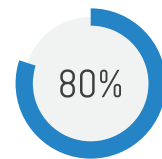
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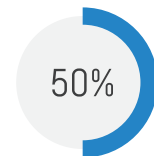


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1
YEAR



- ~ 50% with healthy baseline weight:
overweight/obesity within 5 years of antipsychotic treatment

5
YEARS

Net Positive Impact of Antipsychotics:

- Despite side effects, antipsychotics improve life expectancy in schizophrenia compared to not taking medication.



Factors REDUCING all-cause mortality:

1. Use of antipsychotics
2. ever use of lipid-modifying agents
3. antidepressants
4. lithium

Factors INCREASING all-cause mortality:

1. Cardiovascular disease
2. Liver disease
3. Renal disease
4. Diabetes
5. History of switching antipsychotics
6. Longer duration of previous hospitalizations
7. History of substance abuse
8. ever use of benzodiazepines



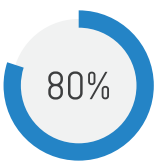
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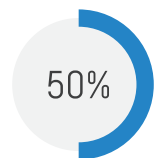


- Rapid & Nonlinear Trajectory



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1
YEAR



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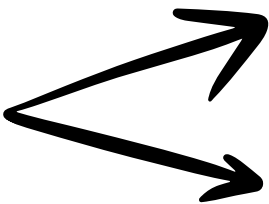
5
YEARS

Net Positive Impact of Antipsychotics:

- Despite side effects, antipsychotics improve life expectancy in schizophrenia compared to not taking medication.



Importance of Treating Antipsychotic-Induced Weight Gain:



- NON-PHARMACOLOGICAL:
- PHARMACOLOGICAL:

- Diet
- Lifestyle interventions.
- Antipsychotic dose adjustments
- Switching medications
- Metformin



CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



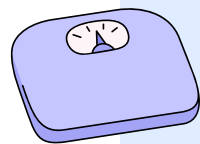
Should Metformin be Used for the Prevention of AIWG?

2022 Cochrane Review:



Results: Metformin was the only pharmacological agent that may be effective for preventing weight gain.

- 17 RCTs (n=1388)
 - Metformin (5)
 - Topiramate (3)
 - H2 antagonists (3)
 - Monoamine modulators (3)
 - Monoamine modulators plus betahistine
 - Melatonin
 - Samidorphan



Recommendation:

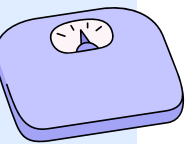
Start metformin around the same time as an antipsychotic.



Add Metformin: (a) at antipsychotic initiation OR
(b) following a switch from one antipsychotic to another

Systematic Review & Meta-analysis:

- Systematic review and meta-analysis of co-commencement of metformin at the time of initiation of an antipsychotic.
- 14 RCTs (11 from Chinese databases). n= 1126
- Metformin group gained on average **3.12 kg**, (95% CI 4.22 kg to 2.01 kg) less than control.
- Clozapine (n = 3), olanzapine (n = 9), risperidone (n = 4) and sulpiride (n = 2) were among the antipsychotics studied.



Large Naturalistic Cohort Study:

- n= 396 (prescribed clozapine)
- Metformin gained on average **3.14 kg** (95% CI .78 kg to 5.52 kg) less weight than the control group at 6 months
- **5.38 kg** (95% CI 2.65 kg to 8.13 kg) less weight at 12 months





CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



What Predictors, Parameters & Thresholds Should Inform the Decision of When to Intervene to Prevent AIWG?

CHOICE OF ANTIPSYCHOTIC:

- Most important nongenetic factor in predicting AIWG.
- Side effect profile is an important factor in the decision making.
- First Episode Psychosis: prefer Low-risk antipsychotics at lowest effective dose.
- If high- or medium-risk antipsychotics used: early use of metformin.
- Clozapine & Olanzapine: highest risk
- Quetiapine, Risperidone & Paliperidone: moderate risks.

Co-commence metformin with medium-risk antipsychotics (quetiapine, paliperidone or risperidone) in the presence of:

- one or more cardiometabolic risk factors OR
- in people aged 10–25 years.

one or more cardiometabolic risk factors:

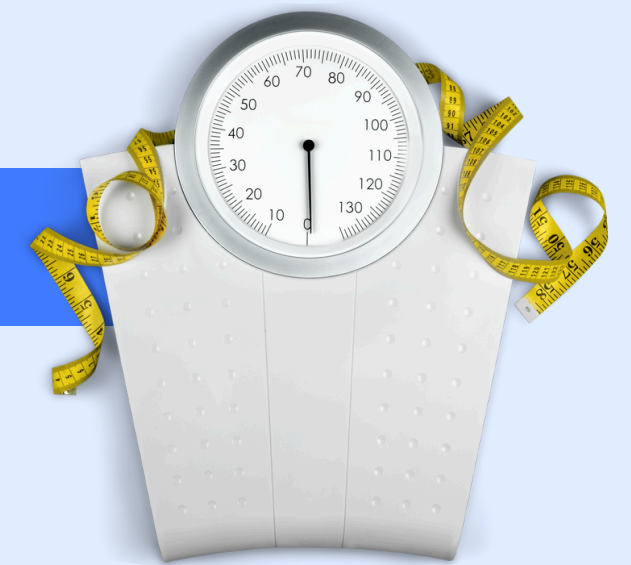
- Hypertension
- Dyslipidaemia
- Diabetes (Type 1 and 2)
- Pre-diabetes (HbA1c 42–47mmol/mol; Fasting glucose 6.1–6.9mmol/L)
- BMI >25 (adjust for ethnicity)
- Age 10–25





ANTIPSYCHOTICS & WEIGHT GAIN

J CLIN PSYCHIATRY . 2023 FEB 8;84(2):22R14490



DOSE RESPONSE

ANTIPSYCHOTICS

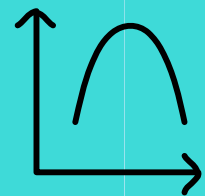
WEIGHT GAIN

ED95

WEEKS

METABOLIC PANELS

QUASI-PARABOLIC



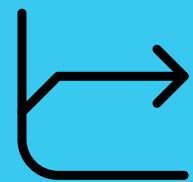
- LURASIDONE
- HALOPERIDOL
- CARIPRAZINE
- BREXPIPIRAZOLE
- QUETIAPINE XR

- 0.53
- 0.66
- 0.80
- 1.11
- 1.40
- 57.93
- 5
- 2.7
- 1.91
- 390.2

- 6
- 5.5
- 6
- 6
- 6

- HDL: ASCEND
- GLUC: ASCEND
- GLUC: ASCEND; LDL & T.COL: DECREASE
- HDL: QUASI-PARABOLIC; T.CHOL: PLATEAU
- SEE IR VS XR COMPARISON

PLATEAU



- ASENAPINE
- RISPERIDONE
- PALIPERIDONE ER
- QUETIAPINE IR
- ILOPERIDONE

- 1.36
- 1.50
- 1.54
- 1.67
- 2.65
- 5.46
- 3.4
- 73.12
- 579.3
- 16.7

- 6
- 5.2
- 12
- 6
- 5

- NO SIGNIFICANT ASSOCIATION
- DATA NOT AVAILABLE
- GLUC: BELL SHAPED
- SEE IR VS XR COMPARISON
- GLUC: ASCEND

ASCENDING



- ARIPIRAZOLE
- PALIPERIDONE
- RISPERIDONE LAI
- ARIPIRAZOLE LAI
- OLANZAPINE
- OLANZAPINE LAI

- 0.88
- 1.73
- 1.95
- 2.61
- 3.61
- 4.29
- 27.2
- 13.8
- 65.37
- 830.13
- 14.95
- 113.7

- 5.5
- 6
- 12
- 12
- 5.75
- 8

- NO SIGNIFICANT ASSOCIATION
- HDL: ASCEND
- DATA NOT AVAILABLE
- QUASI-PARABOLIC
- GLUC & TG: ASCEND; LDL: QUASI-PARABOLIC
- DATA NOT AVAILABLE

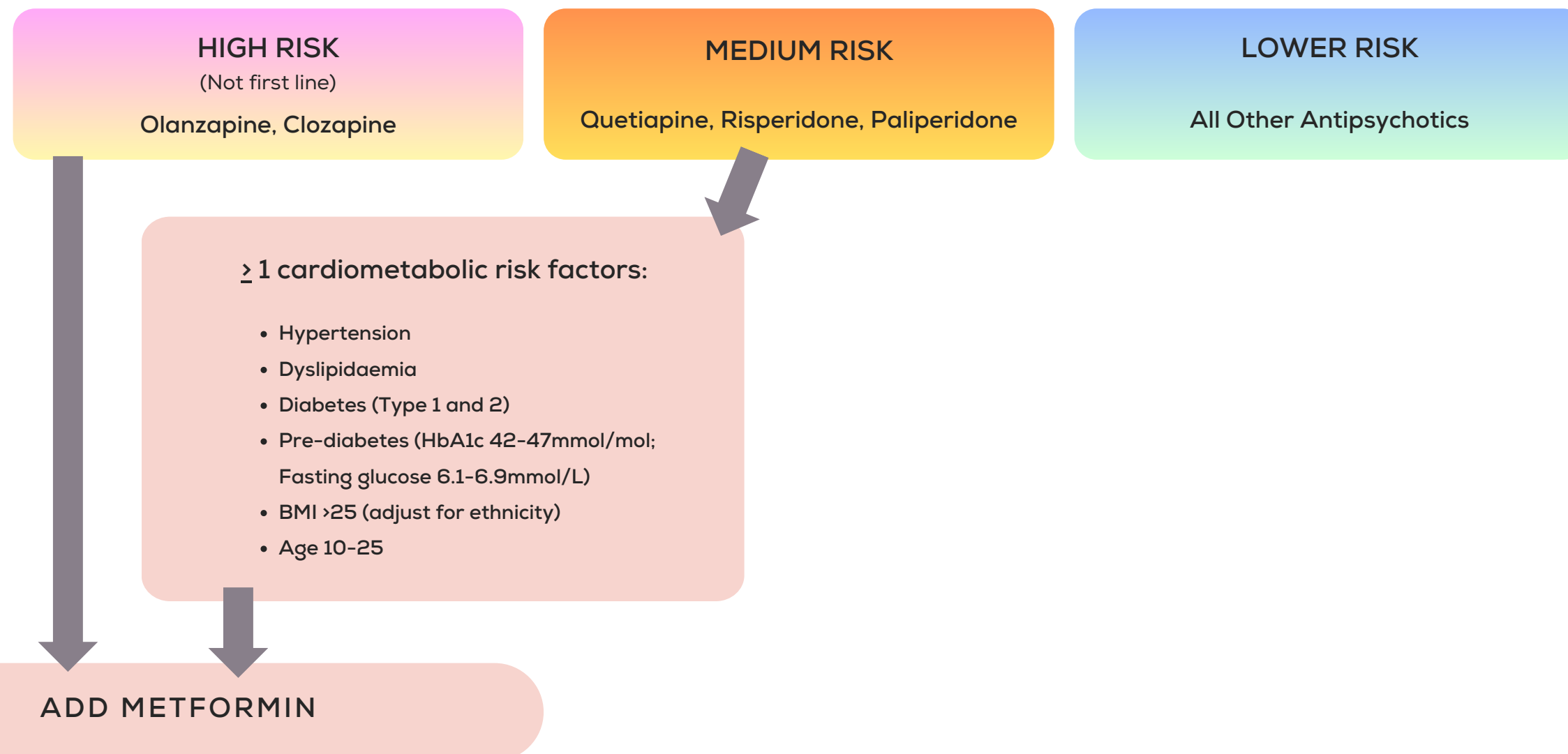
CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



What Predictors, Parameters & Thresholds Should Inform the Decision of When to Intervene to Prevent AIWG?



Add Metformin: (a) at antipsychotic initiation OR
(b) following a switch from one antipsychotic to another



CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?

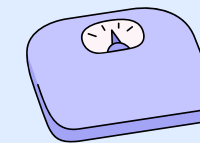


What Predictors, Parameters & Thresholds Should Inform the Decision of When to Intervene to Prevent AIWG?



YOUNG AGE & ANTIPSYCHOTIC NAIVETY:

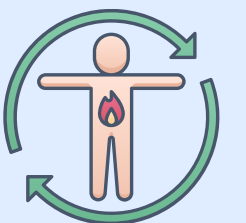
- Younger Age
 - First Episode Psychosis
 - Antipsychotic Naivety
- all predictors for susceptibility to AIWG
- **Age** being a proxy for both **First Episode** and **Antipsychotic Naivety** & vice versa.
 - AIWG rates for Children and adolescents: **2X that seen in adults.**
 - Young and antipsychotic naïve patients: can **gain 3-4-fold more weight** (irrespective of the specific antipsychotic).
 - be mindful of **lower body mass** of children and adolescents.
 - Relevant Predictive Factors for Adults (baseline BMI, gender and ethnicity): were less associated with AIWG in children and adolescents



CARDIOMETABOLIC RISK FACTORS:

Metformin has small to medium effect on cardiometabolic outcomes:

- Total Cholesterol
- Triglycerides
- Fasting Glucose
- HOMA-IR



~1 kg Weight Gain --> CVD Risk increase of 3.1%

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What Predictors, Parameters & Thresholds Should Inform the Decision of When to Intervene to Prevent AIWG?

EARLY TRENDS IN WEIGHT GAIN:

- Weight gain: can be substantial and rapid early in the course of psychosis (**first year of treatment** being critical)
- Individuals with **first episode psychosis**: gained on **average** **3.46 ± 7.81 kg** of weight after a mean of 44.6 days of treatment (*naturalistic cohort study*)
- **Weight Gain and Change in BMI in the 1st weeks of treatment**: most clinically significant factor influencing longer-term risk of adverse cardiometabolic outcomes.

1
YEAR



?
DAYS



EATING BEHAVIOR & EARLY APPETITE INCREASES:

- may predict risk of weight gain: but certainty of evidence is low & inconsistent.
- One study: increased appetite at 4 weeks was associated with significantly greater weight gain at 12 weeks.
- Eating Behavior & Raised Blood Glucose: potential predictors of weight gain.



CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



What Predictors, Parameters & Thresholds Should Inform the Decision of When to Intervene to Prevent AIWG?

THRESHOLD FOR INTERVENTION:

- Threshold for intervention = an increase in baseline body weight of **>3%**
- Children & Adolescents: >3% weight gain outside of the expected trajectory of weight increases
- Age 9–18 years: WHO growth charts should be used to assess expected trajectory weight increases.
- **Recommendation: Commence Metformin with any antipsychotic if >3% increase in baseline body weight is observed during the first year of treatment with an antipsychotic**

3%



>3% weight gained at any time during the first year:

Adults::

- $60\text{Kg} + 3\% = 1.8\text{Kg}$
- $70\text{Kg} + 3\% = 2.1\text{Kg}$
- $80\text{Kg} + 3\% = 2.4\text{Kg}$
- $90\text{Kg} + 3\% = 2.7\text{Kg}$

Young Person:

- >3% weight gained outside expected growth trajectory

CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



Add Metformin: (a) at antipsychotic initiation OR
(b) following a switch from one antipsychotic to another

HIGH RISK

(Not first line)

Olanzapine, Clozapine

MEDIUM RISK

Quetiapine, Risperidone, Paliperidone

LOWER RISK

All Other Antipsychotics

≥ 1 cardiometabolic risk factors:

- Hypertension
- Dyslipidaemia
- Diabetes (Type 1 and 2)
- Pre-diabetes (HbA1c 42-47mmol/mol;
Fasting glucose 6.1-6.9mmol/L)
- BMI >25 (adjust for ethnicity)
- Age 10-25

>3% weight gained at any time during the first year:

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Young Person:

- >3% weight gained outside expected growth trajectory

ADD METFORMIN

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CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



What Dose of Metformin Should be Used for AIWG Prevention?

HOW TO DOSE:

- 500 mg/day to 2 g/day
- Weekly dose increases as tolerated
- BMI/weight or increases in appetite: inform dose escalation schedule
- Take with or after food (minimise GI side-effects)
- Slow release tablet once a day: if GI side-effects persist.
- if GFR 30-44mL/min: max 1g/day

HOW TO DOSE?



AM



PM

WEEK 1

500mg

WEEK 2

500mg

CHECK FOR EFFICACY

WEEK 4

1g

500mg

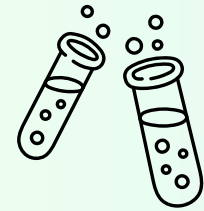
CHECK FOR EFFICACY

WEEK 6

1g

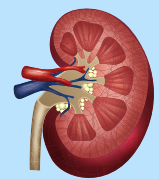
1g

CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



What Monitoring is Recommended with Metformin Treatment?

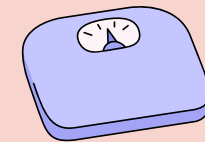
PRE-TREATMENT MONITORING



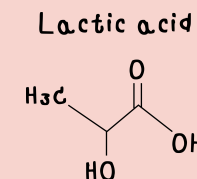
- Renal function (GFR)

- **< 30 mL/min**: Contraindicated
- **30 - 45 mL/min**: Initiation not recommended

ONGOING MONITORING

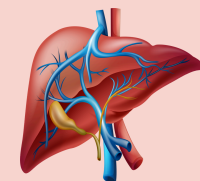


- Weight/BMI



Lactic Acidosis:

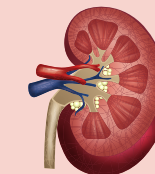
- Watch for symptoms: dyspnea, muscle cramps, abdominal pain, hypothermia, or asthenia.



- Liver function (Annually)



- HbA1c (Annually)



Renal Function (Annually)

Monitor every 6 months for:

- >75 years
- NSAIDs, ACE inhibitors, angiotensin II receptor antagonists, or diuretics



Vitamin B12 (Annually)

Monitor every 6 months for:

- Vegans
- Bariatric surgery
- Older adults
- PPIs
- GI absorption issues

CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



Adverse Events with Metformin

Side-effects: <1 in 10



- Transient - Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite
- Vitamin B12 decrease/deficiency



Side-effects: <1 in 100

- Taste disturbance



Side-effects: <1 in 10,000



- Lactic acidosis
- LFT abnormalities/hepatitis
- Skin reactions: erythema, pruritus, urticaria



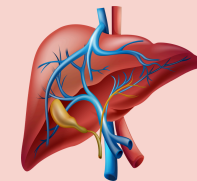
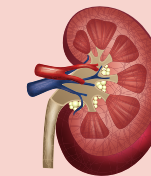
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When Should Metformin be AVOIDED

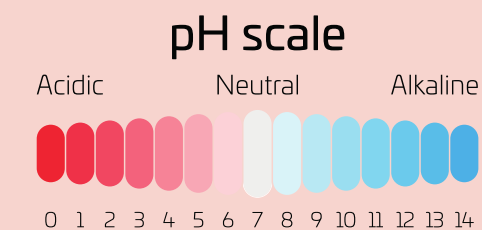
AVOID METFORMIN WITH:

- Severe Renal Failure (GFR < 30 mL/min)



- Hepatic insufficiency

- Acute Metabolic Acidosis



- Alcohol User Disorders Identification Test (AUDIT) score: ≥ 8

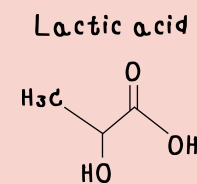
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When Should Metformin be STOPPED

STOP METFORMIN IF:

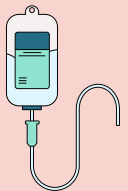
- **Lactic acidosis** is suspected



Risks for lactic acidosis present:

- Dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake)
- Acute alcohol intoxication
- Harmful use of alcohol
- Decompensated heart failure
- Respiratory failure
- Recent myocardial infarction
- Hypovolemic shock
- Severe infection

- Prior to or at the time of administration of iodinated contrast agents (restarted at least 48 hours after)



- GFR drops below 30mL/min



- BMI <20



- Sick day rule - Stop if systemically unwell (restart when well)



- If antipsychotic is stopped





CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



When are GLP-1 Agonists Indicated?

11:26 AM January 28 2025

FDA approves Ozempic® (semaglutide) as the only GLP-1 RA to reduce the risk of worsening kidney disease and cardiovascular death in adults with type 2 diabetes and chronic kidney disease

- *Ozempic® is now indicated to reduce the risk of kidney disease worsening, kidney failure, and death from cardiovascular disease in adults with type 2 diabetes and chronic kidney disease*
- *The approval is based on the results of the pivotal FLOW phase 3b kidney outcomes trial and addresses a critical need for adults with type 2 diabetes living with this common comorbidity of chronic kidney disease*

FDA Approves First Medication for Obstructive Sleep Apnea



For Immediate Release: December 20, 2024

Español

Today, the U.S. Food and Drug Administration approved Zepbound (tirzepatide) for the treatment of moderate to severe obstructive sleep apnea (OSA) in adults with obesity, to be used in combination with a reduced-calorie diet and increased physical activity.

“Today’s approval marks the first drug treatment option for certain patients with obstructive sleep apnea,” said Sally Seymour, M.D., director of the Division of Pulmonology, Allergy, and Critical Care in the FDA’s Center for Drug Evaluation and Research. “This is a major step forward for patients with obstructive sleep apnea.”

For Immediate Release: March 08, 2024

Español

Today, the U.S. Food and Drug Administration approved a new indication for use for Wegovy (semaglutide) injection to reduce the risk of cardiovascular death, heart attack and stroke in adults with cardiovascular disease and either obesity or overweight. Wegovy should be used in addition to a reduced calorie diet and increased physical activity. Cardiovascular disease is a group of diseases of the heart and blood vessels.

“Wegovy is now the first weight loss medication to also be approved to help prevent life-threatening cardiovascular events in adults with cardiovascular disease and either obesity or overweight,” said John Sharretts, M.D., director of the Division of Diabetes, Lipid Disorders, and Obesity in the FDA’s Center for Drug Evaluation and Research. “This patient population has a higher risk of cardiovascular death, heart attack and stroke. Providing a treatment option that is proven to lower this cardiovascular risk is a major advance for public health.”

CAN METFORMIN PREVENT ANTIPSYCHOTIC-INDUCED WEIGHT GAIN?



When are GLP-1 Agonists Indicated?

BMI ≥ 30

BMI 27-30

BMI 27-30 with one of the following:

- Hypertension
- Dyslipidemia
- Diabetes (Type 1 and 2)
- Pre-diabetes (HbA1c 42-47mmol/mol;
Fasting glucose 6.1-6.9mmol/L)
- Obstructive sleep apnea

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HIGH RISK
(Not first line)
Olanzapine, Clozapine

MEDIUM RISK
Quetiapine, Risperidone, Paliperidone

LOWER RISK
All Other Antipsychotics

≥ 1 cardiometabolic risk factors:

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- Dyslipidaemia
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- 90Kg + 3% = 2.7Kg

Young Person:

- >3% weight gained outside expected growth trajectory

ADD METFORMIN

(a) BMI ≥30

(b) BMI 27-30 with one of the following:

- Hypertension
- Dyslipidemia
- Diabetes (Type 1 and 2)
- Pre-diabetes
- Obstructive sleep apnea

ADD GLP-1

IF
UNAVAILABLE

PSYCHIATRY EDUCATION FORUM'S ACADEMY MEMBERSHIP

EMPOWERING MINDS & ENHANCING PSYCHIATRIC CARE



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CLINICAL CASE DISCUSSIONS



DISCOUNTED CME ACCESS

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