



Metformine: de oplossing voor antipsychotica-geïnduceerde gewichtstoename?

MELIA studie

Arts-onderzoeker Nini de Boer, afdeling psychiatrie



UMC Utrecht

Somatiek en Psychiatrie

- **Obesitas risico 4 keer verhoogd**
- **Obesitas prevalentie 50-63%**
- **Levensverwachting 10-20 jaar verlaagd**

Oorzaken overgewicht

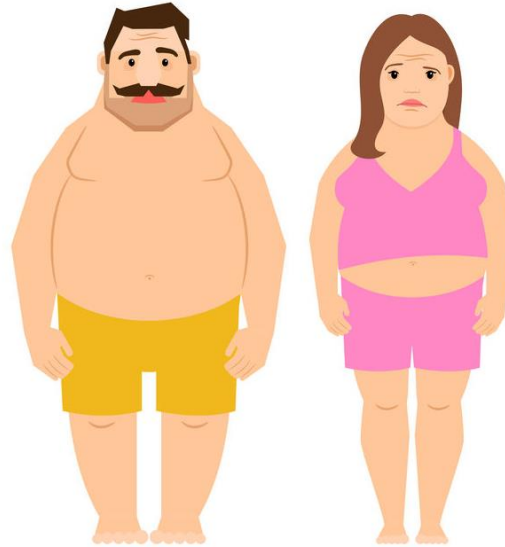
- **Ziekte-gerelateerde factoren**
- **Leefstijl factoren**
- **Genetische factoren**
- **Behandelings-gerelateerde factoren**
 - Antipsychotica-geïnduceerde gewichtstoename

Gewichtstoename bij antipsychotica

↓ Levensverwachting

↓ Therapietrouw

↓ Kwaliteit van leven



↑ Obesitas risico

↑ DM risico

↑ Heropname risico

?



Niet-medicamenteuze interventies



Leefstijlinterventies en gewicht

Outcomes	Intervention	SMD	95% CI	N. trials	N. participants	AMSTAR	AMSTAR Plus Content	Effect size	Between-group p
Weight reduction									<0.001
	Individual lifestyle counseling	-0.98***	-1.15 to -0.81	14	411	8.3	3.7	Large	
	Exercise interventions	-0.96***	-1.27 to -0.66	4	183	8.0	2.5	Large	
	Psychoeducation	-0.77***	-0.98 to -0.55	8	345	8.0	3.0	Medium	
	Dietary interventions	-0.50***	-0.66 to -0.34	22	1,576	8.5	3.5	Medium	
	Group lifestyle	-0.39***	-0.54 to -0.23	19	883	8.3	3.7	Small	
	Cognitive behavioral therapy	-0.37*	-0.55 to -0.18	11	546	8.3	3.7	Small	

Niet-medicamenteuze interventies

Leefstijlinterventies

- Wisselende effectiviteit
- Behoud gewichtsverlies uitdagend
- Implementatie / dagelijkse praktijk

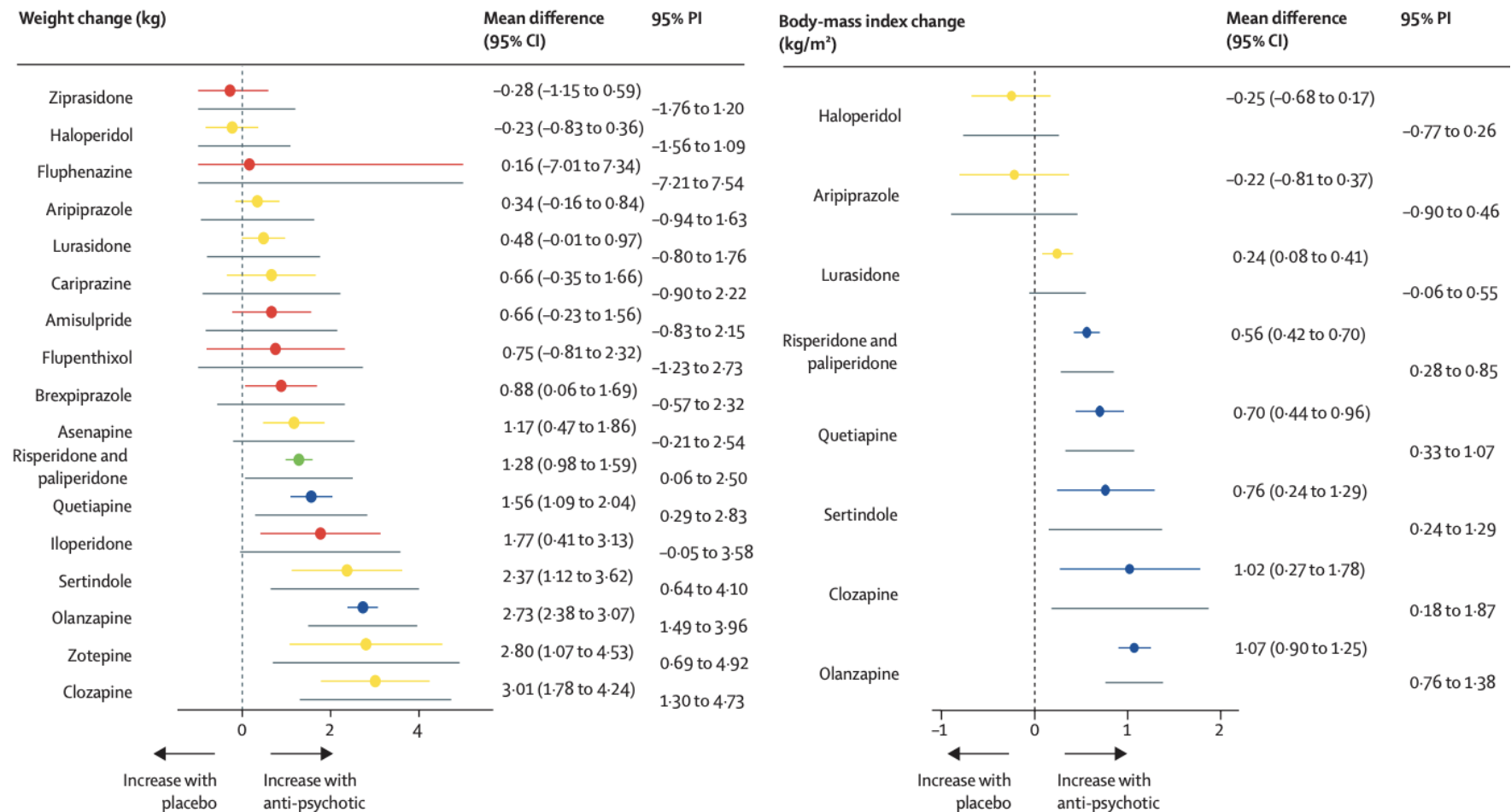
Medicamenteuze interventies

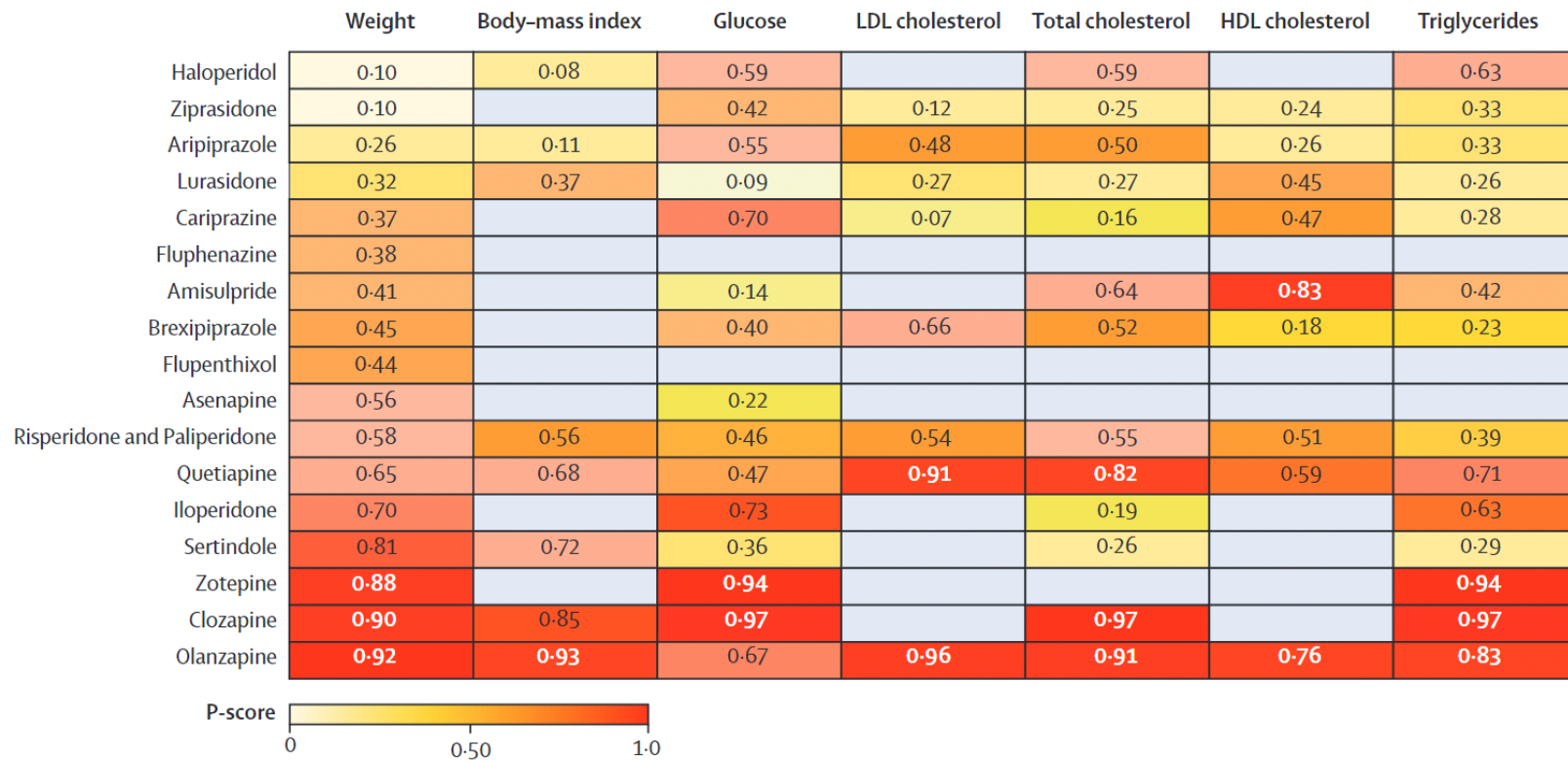
- Antipsychoticum kiezen o.b.v. metabool risicoprofiel indien mogelijk
- Medicatiewissel?
- Toevoegen van farmacologisch middel?
- Dosering verlaging?



Antipsychoticum kiezen o.b.v. metabool risicoprofiel

- Geen gewichtstoename haloperidol, aripiprazol, cariprazine, amisulpride
- Gewichtstoename brexpiprazol, risperidon, quetiapine, olanzapine, clozapine





Medicatiewissel

	Studies	Participants	Statistic	Mean	95% CI	P value	I ²
Switch to Aripiprazole							
Weight (kg)	3	305	MD	-5.52 kg	-10.63 kg to -0.42 kg	.03	97%
Fasting glucose (mg/dl)	2	239	MD	-3.99	-7.34 to -0.64	.02	0%
Triglycerides (mg/dl)	2	239	MD	-31.03	-48.73 to -13.34	.001	0%
HDL cholesterol (mg/dl)	2	239	MD	+2.90	-2.11 to 7.92	.26	70%
Psychotic symptoms	3	301	SMD	-0.44	-1.20 to 0.32	.26	88%
Drop outs	3	334	OR	+1.67	0.59 to 4.73	.33	48%
Switch to Olanzapine							
Weight (kg)	4	353	MD	+2.46 kg	0.34 kg to 4.57 kg	.02	58%
Psychotic symptoms	3	252	SMD	+0.06	-0.23 to 0.35	.70	75%
Drop outs	2	147	OR	+0.86	0.19 to 3.95	.85	69%

Siskind et al. Schizophr. Bull. 2021

- Aripiprazol gewicht -5.52 kg
- Olanzapine gewicht +2.46 kg

Farmacologische additietherapie - geregistreerd

- **Orlistat**
- **Naltrexon/bupropion**
- **Liraglutide**

Farmacologische additietherapie – off label

- **Metformine**
- **Topiramaat**
- **Aripiprazol**
- **GLP-1 receptor agonisten**
- **Olanzapine / Samidorphan**
- **Betahistine**
- **Bupropion**
- **Amantadine**
- **Zonisamide**
- **Pioglitazon**
- **Fluoxetine**
- **H2 receptor antagonisten**
- **Atomoxetine**
- **Intranasaal insuline**
- **Modafinil**
- **Fluvoxamine**
- **Melatonine**
- **Naltrexon**
- **Miricorilant**

Metformine

- **Verhoogt GLP-1 → verminderde eetlust**
- **3 kg gewichtsverlies**
- **Gastro-intestinale bijwerkingen**

Metformine

Outcomes	Intervention	SMD	95% CI	N. trials	N. participants	AMSTAR	AMSTAR Plus Content	Effect size
Weight reduction								
	Metformin	-0.53***	-0.69 to -0.38	29	1,279	8.2	3.6	Medium
Glucose level reduction								
	Metformin	-0.65***	-0.94 to -0.35	17	1,281	9.6	3.7	Medium
Insulin level reduction								
	Metformin	-0.37	-0.81 to 0.07	15	1,007	9.5	4.5	Non-significant
HbA1c reduction								
	Metformin	-0.38*	-0.69 to -0.07	4	383	9.0	6.0	Small

Metformine

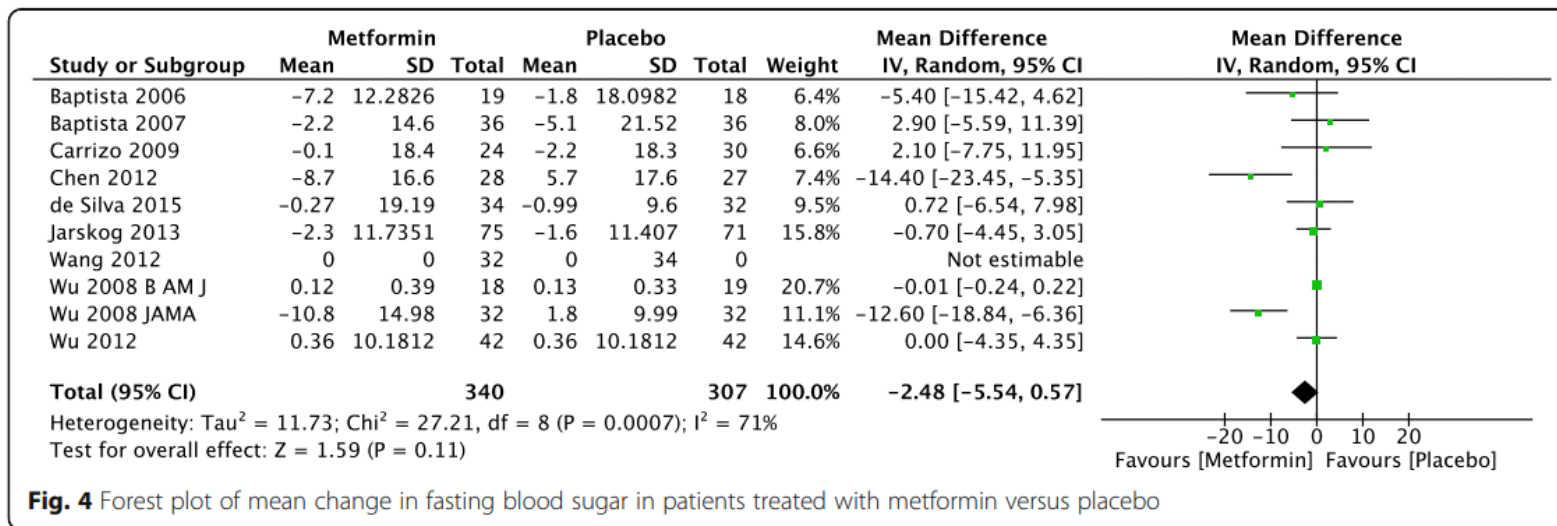


Fig. 4 Forest plot of mean change in fasting blood sugar in patients treated with metformin versus placebo

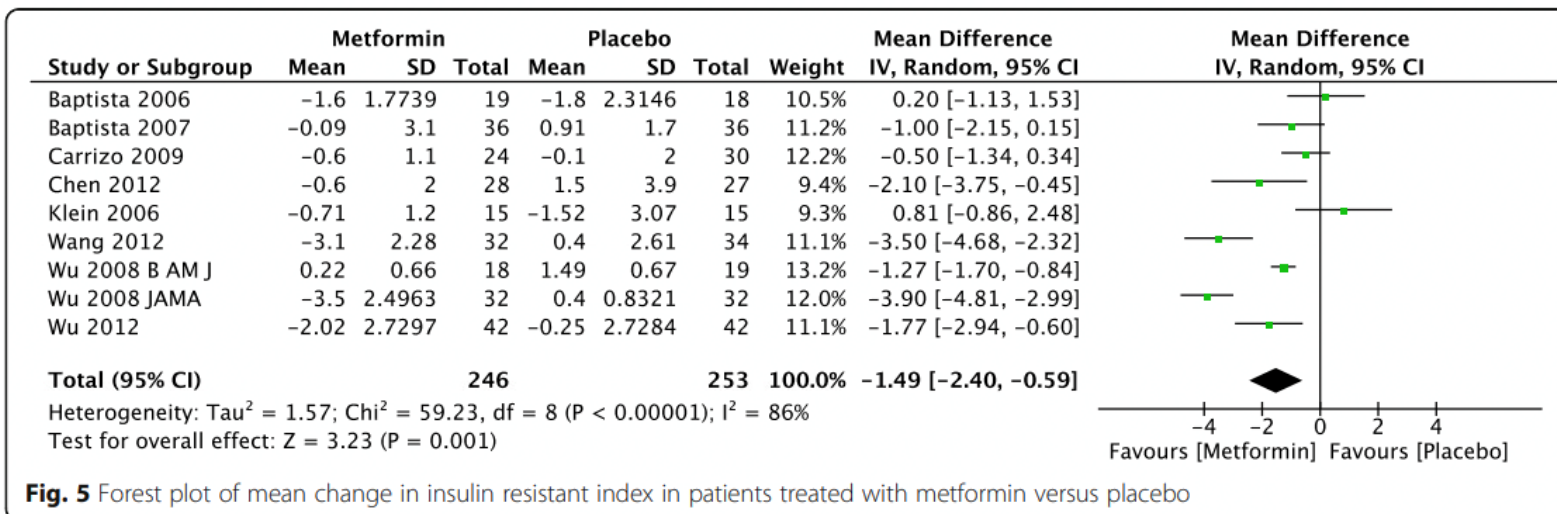


Fig. 5 Forest plot of mean change in insulin resistant index in patients treated with metformin versus placebo

- 3.24kg gewichtsverlies
- Geen vermindering glucose
- Significante vermindering insuline resistentie
- Meer gewichtsverlies first episode vs chronisch (-5.94 kg vs -2.0 kg)

Metformine

- Leefstijl -1.4kg
- Metformine -3.2kg
- Metformine + leefstijl -4.7kg

	Mean (95% Confidence Interval)		
	Week 4	Week 8	Week 12
Lifestyle intervention + metformin (n = 32)			
Weight, kg	62.8 (62.6-63.0) ^a	61.2 (60.6-61.8) ^a	59.8 (58.9-60.7) ^a
BMI	23.9 (23.6-24.0) ^a	23.3 (22.8-23.5) ^a	22.8 (22.5-23.1) ^a
Waist circumference, cm	83.5 (83.2-83.8) ^a	82.9 (82.5-83.3) ^a	84.1 (83.6-84.6) ^a
Fasting glucose, mg/dL	90.1 (88.3-91.9) ^a	86.5 (84.7-88.3) ^a	88.3 (86.5-90.1) ^a
Insulin, μ U/mL	19.9 (18.9-20.9) ^a	16.3 (14.9-17.7) ^a	13.2 (9.0-17.4) ^a
IRI	4.5 (4.2-4.8) ^a	3.5 (2.6-4.4) ^a	2.8 (1.9-3.7) ^a
Metformin (n = 32)			
Weight, kg	63.6 (63.2-64.0) ^a	62.7 (62.1-63.3) ^a	61.9 (61.0-62.8) ^a
BMI	24.2 (24.1-24.3) ^a	23.8 (23.6-24.0) ^a	23.5 (23.2-23.8) ^a
Waist circumference, cm	83.7 (83.4-84.0) ^a	83.3 (82.9-83.7) ^a	82.7 (82.2-83.2) ^a
Fasting glucose, mg/dL	88.3 (86.5-90.1) ^a	84.7 (82.9-86.5) ^a	84.7 (82.9-86.5) ^a
Insulin, μ U/mL	20.1 (19.1-21.1) ^a	16.1 (14.7-17.5) ^a	13.5 (9.3-17.7) ^a
IRI	4.5 (4.2-4.8) ^a	3.4 (2.5-4.3) ^a	2.8 (1.9-3.7) ^a
Lifestyle intervention + placebo (n = 32)			
Weight, kg	63.9 (63.4-64.3) ^a	63.6 (63.0-64.2) ^a	63.4 (62.5-64.3) ^a
BMI	24.0 (23.8-24.2) ^a	23.5 (23.3-23.7) ^a	23.1 (22.8-23.4) ^a
Waist circumference, cm	83.8 (83.5-84.1) ^a	83.7 (83.3-84.1)	83.7 (83.2-84.2)
Fasting glucose, mg/dL	91.9 (90.1-93.7)	90.1 (88.3-91.9) ^a	88.3 (86.5-90.1) ^a
Insulin, μ U/ml	24.3 (23.3-25.4) ^a	23.8 (22.4-25.2) ^a	23.1 (18.9-27.3) ^a
IRI	5.5 (5.2-5.8) ^a	4.9 (4.0-5.8) ^a	4.2 (3.3-5.1) ^a
Placebo (n = 32)			
Weight, kg	65.4 (65.0-65.8) ^a	66.0 (65.4-66.6) ^a	67.2 (66.3-68.1) ^a
BMI	24.7 (24.5-24.8) ^a	24.9 (24.7-25.1) ^a	25.4 (25.1-25.7) ^a
Waist circumference, cm	84.2 (83.8-84.5) ^a	84.7 (84.3-85.1) ^a	85.5 (85.0-86.0) ^a
Fasting glucose, mg/dL	93.7 (91.9-95.5)	91.9 (90.1-93.7)	93.7 (91.9-95.5)
Insulin, μ U/mL	26.6 (25.6-27.6) ^a	27.3 (25.9-28.7) ^a	27.6 (23.4-31.8) ^a
IRI	6.1 (5.9-6.4) ^a	6.2 (5.3-7.1) ^a	6.3 (5.4-7.2) ^a



MELIA STUDIE

*Metformine voor de behandeling van gewichtstoename bij
antipsychotica gebruik*

Studie doel

Metformine en leefstijlinterventies

versus

Placebo en leefstijlinterventies

vergelijken voor de behandeling van gewichtstoename bij antipsychotica

Studie doel

Secundair

Het verschil in metformine-geïnduceerde gewichtsreductie onderzoeken tussen:

- Clozapine versus ander antipsychotica gebruik
- Hoog risico antipsychotica versus ander antipsychotica gebruik

Tertiair

- Kwaliteit van leven
- Metabool syndroom kenmerken
- Algehele mentale en fysieke gezondheid
- Kosten effectiviteit
- Bijwerkingen
- GFR
- Therapietrouw
- Genetische kwetsbaarheid

Inclusie criteria

- Schizofrenie spectrum stoornis / bipolaire stoornis
- Antipsychotica gebruik
- BMI \geq 25
- Bereidheid leefstijlinterventies te ondergaan
- > 16 jaar
- Wilsbekwaam
- Beheersing NL taal

Exclusie criteria

- Neurodegeneratieve extrapiramidale ziekten
- Metformine gerelateerde contra-indicaties
 - condities predisponerend voor weefselhypoxie*
 - metabole acidose*
 - (condities predisponerend voor) nierfalen (GFR <30)*
 - overmatig alcohol gebruik (>3 drinks per day)*
 - lever falen*
- Vitamine B12 deficiëntie
- Diabetes mellitus
- NSAID, ACE-remmer, angiotensine receptor blockers, diuretica, OCT* gebruik
- Zwangerschap / Borstvoeding

Studie opzet

- 128 deelnemers 1 jaar lang volgen
- Randomisatie 26 weken metformine 2000mg/dag of placebo
- 4 studievizites (week 0 – 13 – 26 – 52) – THUISVISITES mogelijk!
- Vragenlijsten, lichamelijk onderzoek, bloedafname
- Reiskostenvergoeding + 10 euro per visite

Studie procedures

Vragenlijsten

M.I.N.I. plus

CGI

EQ-5d-3L

WHOQOL-BREF

CAPE

BPRS

iPCQ

iMCQ

PAVS

SIMPAQ

- Mini International Neuropsychiatric Interview
- Clinical Global Impression
- EuroQol Quality of Life scale
- World Health Organization Quality of Life scale
- Community Assessment of Psychic Experiences
- Brief Psychiatric Rating Scale
- Productivity Cost Questionnaire
- Medical Consumption Questionnaire
- Physical Activity Vital Sign Questionnaire
- Simple Physical Activity Questionnaire

Lichamelijk onderzoek

- Lichaamsgewicht, lengte, BMI, middelomtrek, bloeddruk
- Fysiek uithoudingsvermogen (6MTWT)

Lab procedures

- Bloedafname (GFR, LDL, HDL, triglyceriden, insuline, glucose, HbA1c, GFR)
- Optioneel DNA extractie (bloed of speeksel)

Leefstijlinterventies

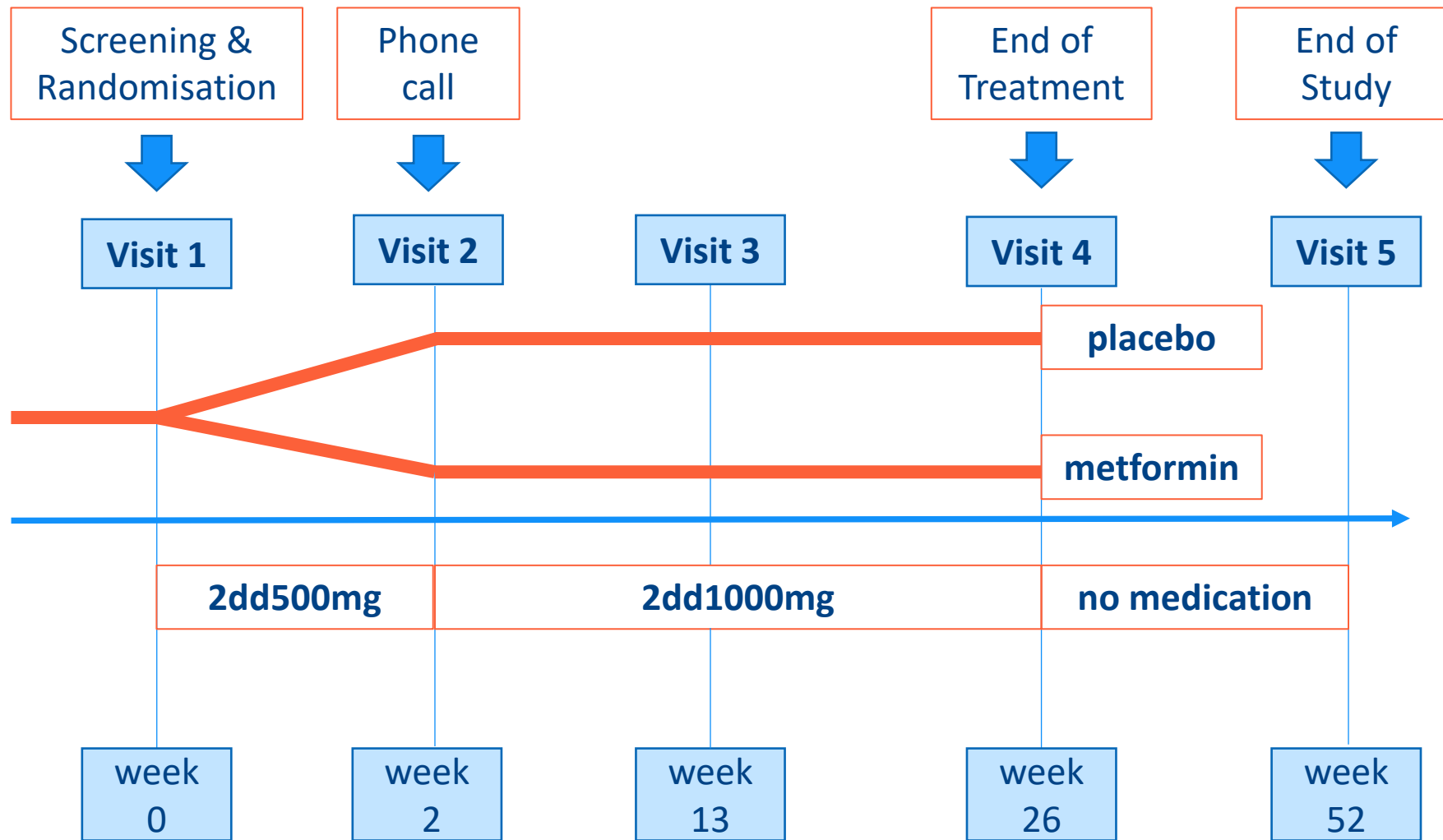
Dieetadviezen

- (Online) consulten dietist *Careyn*
- Online voedingsvragenlijst (WUR Eetscore)

Bewegingsprogramma

- 60 minuten per week ongesuperviseerd bewegen
- Online wekelijkse sportlessen onder supervisie (pilates of fitness)

Deelnemers mogen op elk moment stoppen met leefstijlinterventies en doorgaan met studiedeelname!



Inclusies

- **Inclusie periode tot 1 April 2023**
- **95 inclusies**
- **Doel 120 inclusies**

Verwijzen deelnemers

Geschikte patient?

- Vraag toestemming voor het delen van contactgegevens met MELIA
- E-mail contact gegevens naar melia@umcutrecht.nl of bel 088-7567412

MELIA onderzoekers benaderen de patient, beoordelen de geschiktheid en voeren IC procedures en studievizites uit

Metformine

- Significant minder kans op >5% gewichtstoename (12.5% versus 80%)
- Significant meer kans op gewichtsverlies (37.5% versus 0%)
- HbA1c en diastolische bloeddruk significant verlaagd

Siskind et al. Therapeutic Advances in Psychopharmacology 2021

	Metformin, (n = 8)*	Placebo, (n = 5)*	p value
Change in weight			
Weight gain	5 (62.5%)	5 (100%)	0.024
Weight loss	3 (37.5%)	0 (0%)	
5% weight gain			
≥5% weight gain	1 (12.5%)	4 (80%)	0.015
<5% weight gain	7 (87.5%)	1 (20%)	

Topiramaat

Vancampfort et al. World Psychiatry 2019

Outcomes	Intervention	SMD	95% CI	N. trials	N. participants	AMSTAR		Effect size
						AMSTAR	Plus Content	
Weight reduction	Topiramate	-0.72***	-1.56 to -0.33	15	783	10.0	3.0	Medium
Glucose level reduction	Topiramate	-0.43	-1.00 to 0.14	6	369	10.0	3.0	Non-significant
Triglycerides reduction	Topiramate	-0.68*	-1.23 to -0.13	5	268	10.0	3.0	Medium
LDL-cholesterol reduction	Topiramate	-0.80***	-1.06 to -0.53	4	247	10.0	3.0	Large

- Significante vermindering gewicht, triglyceriden, ldl
- Geen vermindering glucose, hdl en totaal cholesterol
- **Significant meer paresthesie**

Aripiprazol

Vancampfort et al. World Psychiatry 2019

Outcomes	Intervention	SMD	95% CI	N. trials	N. participants	AMSTAR		Effect size
						AMSTAR	Plus Content	
Weight reduction	Aripiprazole augmentation	-0.73***	-0.97 to -0.48	9	813	8.3	3.0	Medium
Glucose level reduction	Aripiprazole augmentation	-0.34***	-0.47 to -0.20	10	710	9.3	3.5	Small
Triglycerides reduction	Aripiprazole augmentation	-0.17**	-0.30 to -0.04	9	631	9.5	3.5	Negligible
Total cholesterol reduction	Aripiprazole augmentation	-0.32***	-0.47 to -0.17	10	692	9.3	3.5	Small

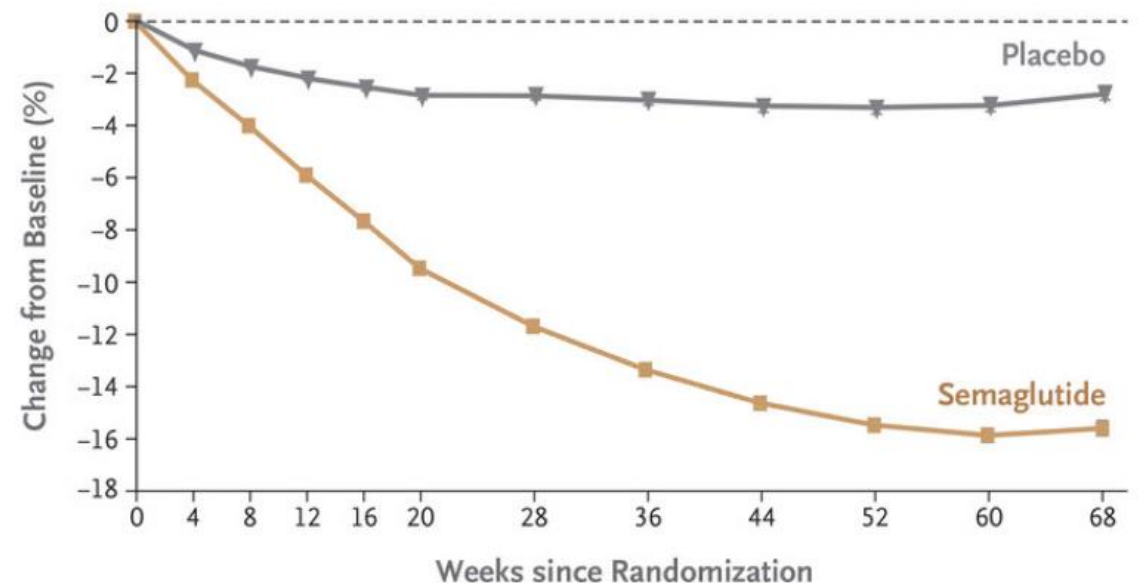
- Significante vermindering gewicht, glucose, totaal cholesterol
- Geen vermindering ldl, hdl, triglyceriden
- **Significant meer agitatie/ acathisie en angst**

Semaglutide

- 15.3 kg gewichtsverlies
- Verlaging glucose -8.35mg/dl
- Verbetering cholesterolwaarden
- Wekelijks s.c. injecties
- Gastro intestinale bijwerkingen
- Onvoldoende bewijs EPA

Wilding et al. N Engl J Med 2021

Body Weight Change from Baseline by Week, Observed In-Trial Data



Overige middelen – onvoldoende bewijs

- Amantadine
- Zonisamide
- Pioglitazon
- Fluoxetine
- H2 receptor antagonisten
- Atomoxetine
- Intranasaal insuline
- Modafinil
- Aripiprazol
- Fluvoxamine
- Melatonine
- Naltrexon
- Miricorilant
- Betahistine
- Bupropion
- Samidorphan/ olanzapine

Gewichtstoename bij antipsychotica?*

Start leefstijlinterventies

Leefstijlinterventies onhaalbaar of onvoldoende resultaat?

JA

NEE

Antipsychoticum met hoog metabool risicoprofiel?

Continueren leefstijlinterventies

JA

NEE

Overweeg wissel naar antipsychoticum met laag metabool risicoprofiel (voorkeur aripiprazol; evt. i.c.m. leefstijlinterventies)**

OF

Overweeg off-label farmacologische additietherapie (voorkeur metformine; evt. i.c.m. leefstijlinterventies)***


Overweeg off-label farmacologische additietherapie (voorkeur metformine; evt. i.c.m. leefstijlinterventies)***

STUDY PROTOCOL

Open Access

Study protocol of a randomized, double-blind, placebo-controlled, multi-center trial to treat antipsychotic-induced weight gain: the Metformin-Lifestyle in antipsychotic users (MELIA) trial



Nini de Boer^{1*} , Sinan Guloksuz^{2,3}, Caroline van Baal⁴, Leonie Willebrands¹, Jeroen Deenik^{1,2,5}, Christiaan H. Vinkers^{6,7}, Inge Winter-van Rossum¹, Janneke Zinkstok¹, Ingeborg Wilting⁸, Jasper B. Zantvoord⁶, Frank Backx⁹, Wilma E. Swildens^{10,11}, Marieke Schouw¹⁰, Jan Bogers¹², Folkwin Hulshof¹³, Rudolf de Knijff¹³, Peter Duindam¹³, Mike Veereschild¹³, Maarten Bak^{2,14}, Geert Frederix¹⁵, Lieuwe de Haan^{6,16}, Jim van Os^{12,17}, Wiepke Cahn^{1,10} and Jurjen J. Luyckx^{1,3,18}

Abstract

Background: Antipsychotic-induced Weight Gain (AIWG) is a debilitating and common adverse effect of antipsychotics. AIWG negatively impacts life expectancy, quality of life, treatment adherence, likelihood of developing type-2 diabetes and readmission. Treatment of AIWG is currently challenging, and there is no consensus on the optimal management strategy. In this study, we aim to evaluate the use of metformin for the treatment of AIWG by comparing metformin with placebo in those receiving treatment as usual, which includes a lifestyle intervention.

Methods: In this randomized, double-blind, multicenter, placebo-controlled, pragmatic trial with a follow-up of 52 weeks, we aim to include 256 overweight participants (Body Mass Index (BMI) > 25 kg/m²) of at least 16 years of age. Patients are eligible if they have been diagnosed with schizophrenia spectrum disorder and if they have been using an antipsychotic for at least three months. Participants will be randomized with a 1:1 allocation to placebo or metformin, and will be treated for a total of 26 weeks. Metformin will be started at 500 mg b.i.d. and escalated to 1000 mg b.i.d. 2 weeks thereafter (up to a maximum of 2000 mg daily). In addition, all participants will undergo a lifestyle intervention as part of the usual treatment consisting of a combination of an exercise program and dietary consultations. The primary outcome measure is difference in body weight as a continuous trait between the two arms from treatment inception until 26 weeks of treatment, compared to baseline. Secondary outcome measures include: 1) Any element of metabolic syndrome (MetS); 2) Response, defined as ≥5% body weight loss at 26 weeks relative to treatment inception; 3) Quality of life; 4) General mental and physical health; and 5) Cost-effectiveness. Finally, we aim to assess whether genetic liability to BMI and MetS may help estimate the amount (Continued on next page)

Vragen?

**Verwijzen van mensen met schizofrenie spectrum stoornis/
bipolaire stoornis, overgewicht en antipsychotica?**

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088-7567412

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- dr. Sinan Guloksuz

MELIA leefstijlinterventies

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- Marloes Nieberg (SPATverandert)
- Careyn dietisten Utrecht

Dit project wordt medemogelijk gemaakt door



Dit project is opgestart door



Deelnemende centra:



Mondriaan

