The MEtformin-LIfestyle in Antipsychotic users trial (MELIA): optimizing the use of metformin in the management of antipsychotic-induced weight gain.

Published: 14-05-2020
Last updated: 30-01-2025

Objective: We aim to optimize the application of an existing drug, metformin, for a new indication, AiWG, by showing that metformin in combination with lifestyle interventions reduces AiWG compared to placebo in combination with lifestyle...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52718

Source
ToetsingOnline

Brief title
MELIA

Condition

- Other condition
- Schizophrenia and other psychotic disorders

Synonym
Antipsychotic induced Weight Gain

Health condition

gewicht

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Antipsychotic, Lifestyle, Metformin, Weight gain

Outcome measures

Primary outcome

Primary Objective: We aim to optimize the application of an existing drug, metformin, for a new indication, AiWG, by showing that metformin in combination with lifestyle interventions reduces the AiWG compared to placebo in combination with lifestyle interventions.

Secondary outcome

Secondary objective: We aim to investigate the difference in reduction of AiWG between clozapine use versus other antipsychotic use, betweeen patients with schizophrenia and bipolar disorder and the difference between high-risk agents -risperidone, olanzapine, clozapine and quetiapine- vs. all other antipsychotics.

In post hoc sensitivity analysis, the quantitative measure of the amount of self-reported AiWG will be used to examine differences between AiWG and weight gain due to other reasons.

Tertiary objective: At last, we aim to assess whether metformin compared to

placebo improves metabolic traits, quality of life, general physical and psychological health, cost effectiveness and whether genetic liability to BMI and metabolic syndrome may help estimate weight reduction following initiation of metformin treatment.

Study description

Background summary

Rationale: Antipsychotics are the mainstay treatment modality for schizophrenia and are also indicated for treatment of bipolar disorder. Of the insidious adverse drug reactions (ADRs) to antipsychotics, Antipsychotic-induced Weight Gain (AiWG) is the most debilitating and prevalent ADR. AiWG negatively impacts life expectancy, quality of life, treatment adherence, chances of developing type-2 diabetes and likelihood of readmission. Treatment of AiWG is currently very challenging and few interventions have been investigated in well powered trials of sufficient quality.

Metformin is a very promising agent in the treatment of AiWG. Metformin generally promotes satiety and increases Glucagon-like Peptide (GLP-1), thus often resulting in reduced energy intake. Meta-analyses conclude that of all agents studied as monotherapy, metformin is most effective (albeit still of limited benefit) in attaining weight loss for child and adolescent schizophrenia patients and for those patients who use clozapine.

In sum, treatment of AiWG is currently very challenging and few interventions have been investigated in well powered trials of sufficient quality.

We aim to optimize the application of an existing drug, metformin, for a new indication, AiWG, by showing that metformin in combination with lifestyle interventions reduces AiWG compared to placebo in combination with lifestyle interventions.

For more information see chapter 1 and 2 in the protocol.

Study objective

Objective: We aim to optimize the application of an existing drug, metformin, for a new indication, AiWG, by showing that metformin in combination with lifestyle interventions reduces AiWG compared to placebo in combination with lifestyle interventions. The following subgroup analyses within subtypes of

patients will be conducted using the same model to explore possible differences in treatment effects: those on clozapine vs. those on other antipsychotics, those with bipolar disorder versus schizophrenia spectrum disorder and those on high-risk agents -risperidone, olanzapine, clozapine and quetiapine- vs. all other antipsychotics.
In post hoc sensitivity analysis, the quantitative measure of the amount of self-reported AiWG will be used to examine differences between AiWG and weight gain due to other reasons. At last, we aim to assess whether metformin compared to placebo improves metabolic traits, quality of life, general physical and psychological health, cost effectiveness and whether genetic liability to BMI and metabolic syndrome may help estimate weight reduction following initiation of metformin treatment.

Study design

Study design: A randomized, double blind, multicenter, placebo-controlled, pragmatic trial.

The pragmatic design of MELIA allows for a comparison of the efficacy of lifestyle interventions (i.e. exercise training and consultations with a dietician) with or without concomitant use of metformin in the treatment of Antipsychotic induced Weight Gain (AiWG).

We will conduct a pragmatic, randomized, double blind, placebo-controlled multicenter trial of metformin in patientswith schizophrenia/ bipolar disorder suffering from AiWG and undergoing lifestyle interventions. The estimated length of the study will be 3.5 years (including a participants* enrolment phase) and participants will be followed-up for one year. This design was chosen to investigate the possible added value of metformin over lifestyle interventions and to align the design as much as possible with clinical practice where lifestyle interventions are offered in most institutes across the country for patients on antipsychotics who suffer from relatively high weight. Lifestyle interventions are standardized across sites as follows. This will be a combination of an exercise program and dietary interventions. The dietary intervention consists of five consultations with a dietician (referral by G.P.) to ensure both healthy food and appropriate caloric intake and measurement of weight, BMI and waist circumference. The exercise program consists of minimally 60 minutes per week of unsupervised exercise by choice, i.e. walking, dancing or jogging, either privately, group endurance workouts or strength training. Furthermore, participants gather in weekly lifestyle group sessions under supervision of a lifestyle coach including weekly weight measurements and assessment of physical activity using the Physical Activity Vital Sign questionnaire (PAVS). During those sessions participants perform a low-intensity exercise, such as strolling, reflect how their exercise program and dietary interventions are getting along, report whether they exercised 60 minutes that week, and provide tips to one another about how to overcome certain barriers. Participants may wish to discontinue lifestyle interventions

at any moment and still continue with the current trial. Similarly, patients may continue with the trial after switching or stopping antipsychotic use.

Participants will undergo four main, face-to-face visits, as well as one short telephone visit. Every face to face study visit multiple questionnaires are done, blood tubes are drawn and physical examination is done including weight, waist circumference, blood pressure and a physical endurance test. One year after the first study visit body weight, waist circumference, blood pressure and physical endurance are measured and medication use is assessed during a 20 minute follow-up visit.

Week 0- Visit 1 - Face to face visit, screening & randomisation. Start dose 500mg B.I.D.
Week 2 - Visit 2 - Phone call visit, dose and side effects verification and evaluation. Dose 1000 mg B.I.D.
Week 13 - Visit 3 Face to face visit.
Week 26 - Visit 4 Face to face visit.
Week 52 - Visit 5 Face to face visit (not included in flowchart).

Questionnaires done during face-to-face visits:
M.I.N.I. plus section M
WHOQOL-BREF
EQ-5D-3L
CGI
PHQ
BPRS
CAPE
6MTWT
iPCQ
iMCQ
SIMPAQ

If participants want to stop taking study medication before the end of the study and similarly do not want to revoke their informed consent, they will be offered a naturalistic follow up. Participants thus may quit taking studymedication and still continue with the study visits and procedures conform this protocol. If participants do not want to continue with study visits after quitting studymedication before the end of the study and similarly do not want to revoke their informed consent, the primary outcome of this study (weight) will be requested at the G.P. or treating physician, psychiatrist or psychiatric nurse after 3 and/ or 6 months and/or 12 months after study medication initiation after obtaining written informed consent of the participant by the research-physician.

For more information see chapter 3 in the protocol.

Intervention

Intervention (if applicable): Metformin or placebo started at 2dd500mg and then increased to 2dd1000mg after two weeks.

Study burden and risks

The risks associated with participation are minimal considering the wide experience, well known safety profile and generally mild side effect profile of metformin. The burden for participants consists of taking medication daily (either placebo or metformin), one short telephone visit of five minutes, three face-to-face visits of approximately 20-120 minutes during which questionnaires are filled out, three blood tubes are drawn, physical examination and a physical endurance test are done, and one face-to-face visit of 20 minutes one year after the first study visit. Their weight and waist circumference will be assessed during all live visits. Except for the blood draw and time investment, also including travelling to the institute, we expect no physical or physiological discomfort associated with participation. We do not include incapacitated persons in our study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

- Diagnosis of schizophrenia spectrum disorders according to DSM-IV-TR or DSM-5 criteria;
- Diagnosis of bipolar disorder according to DSM-IV-TR or DSM-5 criteria;
- Antipsychotic use for at least 3 months (participants may have switched antipsychotic use in the past 3 months)
- Willingness to undergo lifestyle interventions;
- Dutch speaking and reading;
- Mentally competent;
- At least 16 years of age;
- Overweight (BMI >25).

Exclusion criteria

- Suffer from neurodegenerative extrapyramidal disease;
- Carry metformin-related contra-indications, i.e.: conditions predisposing to tissue hypoxia (such as congestive heart failure, recent myocardial infarction and respiratory failure), metabolic acidosis, precoma diabeticum, kidney failure (GFR<30ml/min) and conditions predisposing to kidney failure, liver failure and disorders in the use of alcohol defined as > 2 reported consumptions daily and a gGT of over 60U/L or a CDT >2.2% (measured in blood using the N-Latex CDT method).
- Use of one or more of the following medication(s):
NSAIDs
ACE-inhibitors
ARBs (angiotensin receptor blockers)
diuretics
OCT (organic cation transporters) -1 and 2 inhibitors (e.g. cimetidine, dolutegravir, isavuconazol, trimethoprim, vandetanib, crizotinibib, vandetanib, and verapamil) and inductors (e.g. rifampicin);
- Suffer from vitamin B12 deficiency;
- Suffer from diabetes mellitus;
- Pregnant or breast feeding women or fertile women refusing contraceptive use.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	09-03-2021
Enrollment:	256
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Metformin
Generic name:	Metformin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	14-05-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-07-2020
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	25-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-000053-27-NL
CCMO	NL72987.041.20
Other	NL8440