The effect of MElatonin on Depression, Anxiety, CIrcadian and Sleep disturbances in patients after acute myocardial syndrome.
The MEDACIS trial: protocol for a randomized, placebo-controlled, double-blinded trial.

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INTRODUCTION

Background
The prevalence of major depression disorder following acute coronary syndrome (ACS) has been reported to be approximately 20% as assed by structured clinical interviews. However, a prevalence, as high as 50 %, has been reported with different depression questionnaires.
Depression following ACS has been associated with a 2-2.38 (OR) increase in all-cause mortality, and 2.5-2.7 (OR) cardiac mortality within 24 months of the primary event. Depression was by the American Heart Association (AHA) recently categorized as an independent risk factor for adverse medical outcomes in patients after acute coronary syndrome (ACS). Furthermore, the AHA has made recommendations of implementing screening for depression in the post MI period.
A previous study has shown a prophylactic effect of SSRI prescribes to paitents following ACS over a 1 year period. However, SSRI has also been shown to be associated with sleep disturbances, sexual disturbances and arythmias. Therefore, an intervention which could allivate depression following ACS with the lowest incidence of side-effect would be of great clinical interest.

Aim
The aim of the current study is the antidepressant effect of melatonin in patient following ACS used in a prophylactic setup. Secondary aims will be to investigate the effect of melatonin on anxiety, sleep and circadian rhythm.

METHODS

The MEDACIS trial is a randomised, placebo-controlled, double-blinded multicenter trial investigating the effect of 25 mg exogenous melatonin (intervention group) against placebo (control group) and the study is designed as a parallel group superiority trial.

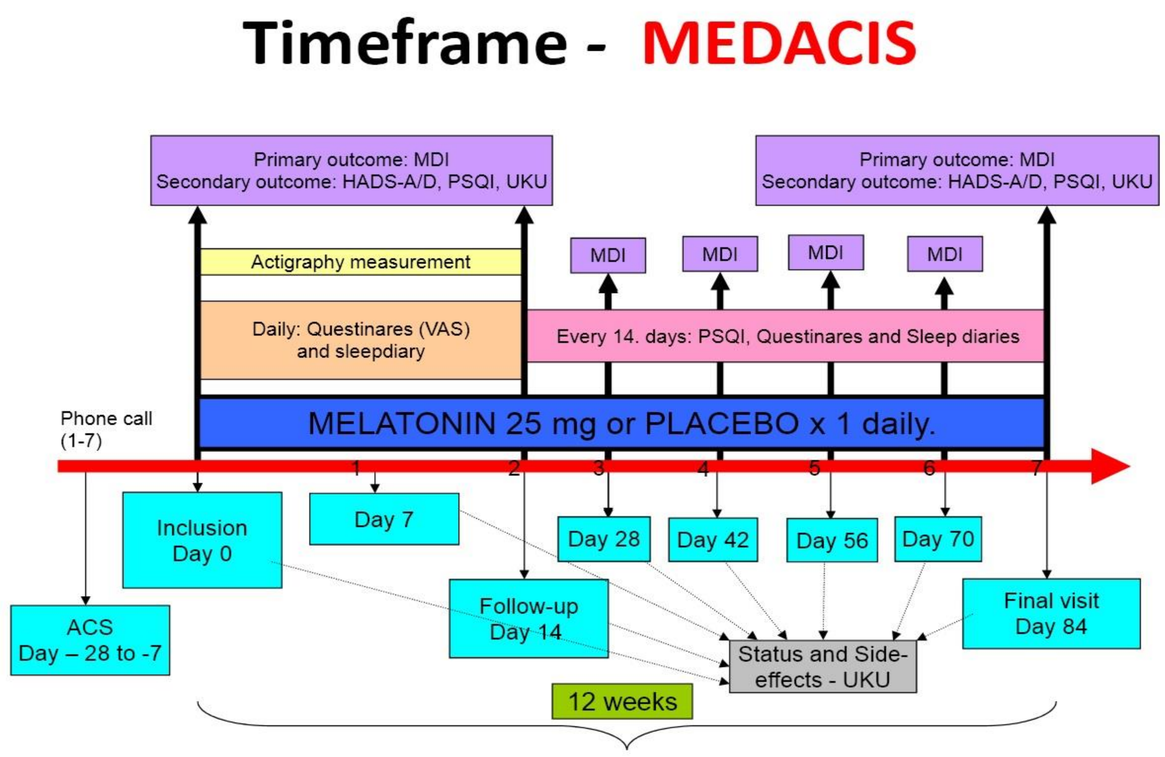
Primary effect parameter
- MDI (Major Depression Inventory) every 2 weeks

Secondary effect parameter
- Hospital anxiety and depression scale (HADS-A and HADS-D)
- Sleep and circadian outcomes measured by actigraphy.
- Sleep quality measured by Pittsburgh sleep quality index (PSQI)
- Safety, Side-effects and compliance to study medication (UKU).

Tertiary effect parameter
- Sleep diary
- Sleep, pain, anxiety, fatigue, and general well-being measured by VAS.
- Blood work – Circadian clock genes

Inclusion criteria
1. Patients should be admitted to a coronary care unit for ACS, and should be enrolled at the latest 4 weeks after the primary ACS.
2. Participants should be 18 years or older.
3. No sign of depression on MDI at the point of enrolment.
4. Participants must sign an informed consent form
5. Females not in menopause (defined as no menstruation during the last 12 months) should have a negative pregnancy test. Furthermore, reproductive females should use a secure birth control.

TIMEFRAME



METHODS

Exclusion criteria
A total of 14 exclusion criteria are related to the trial. Most important are:

- Ongoing or previous pharmacological treated depression or bipolar disorder is not allowed.
- At the point of inclusion no participation in another pharmacological intervention trial is allowed.
- No immunological disease is allowed,
- Severe liver disease defined as transaminases above X 3 normal levels, and severe kidney disease defined as eGRF under 40 ml/min.
- Ongoing hypnotic treatment.
- Known sleep disorder (e.g. insomnia, restless legs etc.)
- Severe, life-threatening medical condition, that implies that the patient cannot participate in the study course. (e.g. cancer, stroke)
- Indication for coronary artery bypass graft (CABG).

Sample size
Sample size is calculated on the basis of a conservative assumption that, 31 % of patients following ACS will develop depressive symptoms which we assume can be reduced to 15.5 % by melatonin treatment. Power calculation is based on two-sided test, and with a power of 0.80 and the significance level 5 % (alfa= 0.05), the required sample size in each group is 116. There are no interim efficacy analyses planned. The patients will be randomized in blocks of 6 and therefore the study will proceed until 120 patients have been enrolled in each arm.

STATUS OF THE TRIAL

The trial has gotten all approval from the authorities. On the basis of retrospective analysis from the 3 recruiting centers in Region Zealand the relevant patient population is available to complete the study within the planned study period.
The study is planed to start in the end of 2015 and last patient last visit is planned for the 30 November 2017.

The study has been registered at clinicaltrial.gov : NCT02451293

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