



The effect of MELatOnin on Depression, anxiety, cognitive function and sleep disturbances in patients with breast cancer. The MELODY trial: protocol for a randomized, placebo-controlled, double-blinded trial.

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000647
Article Type:	Protocol
Date Submitted by the Author:	18-Nov-2011
Complete List of Authors:	Hansen, Melissa; Herlev Hospital, University of Copenhagen, Department of Gastroenterology, Surgical Section Madsen, Michael; Herlev Hospital, University of Copenhagen, Department of Gastroenterology, Surgical Section Hageman, Ida; Rigshospitalet, University of Copenhagen, Psychiatric Center Copenhagen Rasmussen, Lars; Rigshospitalet, University of Copenhagen, Department of Anaesthesia, Centre of Head and Orthopaedics Bokmand, Susanne; Herlev Hospital, University of Copenhagen, Department of Breast Surgery Rosenberg, Jacob; Herlev Hospital, University of Copenhagen, Department of Gastroenterology, Surgical Section Gögenur, Ismail; Herlev Hospital, University of Copenhagen, Department of Gastroenterology, Surgical Section
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology, Pharmacology & therapeutics
Keywords:	Breast surgery < SURGERY, Depression & mood disorders < PSYCHIATRY, Delirium & cognitive disorders < PSYCHIATRY, SLEEP MEDICINE, Anxiety disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS

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Title page – study protocol

The effect of MELatOnin on Depression, anxiety, cognitive function and sleep disturbances in patients with breast cancer. The MELODY trial: protocol for a randomized, placebo-controlled, double-blinded trial.

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Key words: breast cancer, melatonin, depression, sleep disturbances, cognitive function

Word count: 2959

ABSTRACT

Introduction: Breast cancer represents about one third of all cancer diagnoses and accounts for about 15 % of cancer deaths in women. Many of these patients experience depression, anxiety, sleep disturbances and cognitive dysfunction. This may adversely affect quality of life but also contribute to morbidity and mortality. Melatonin is a regulatory circadian hormone having, among others, a hypnotic and an anti-depressive effect. It has very low toxicity and very few adverse effects compared with the more commonly used antidepressants and hypnotics.

Methods and analysis: The objective of this double-blind randomized, placebo-controlled trial is to investigate whether treatment with oral melatonin has a prophylactic or ameliorating effect on depressive symptoms, anxiety, sleep disturbances and cognitive dysfunction in women with breast cancer. Furthermore we will examine whether a specific clock-gene PER3 is correlated with an increased risk of depressive symptoms, sleep disturbances or cognitive dysfunction.

The MELODY-trial is a prospective double-blinded, randomized, placebo-controlled trial in which we intend to include 260 patients. The primary outcome is depressive symptoms measured by the Major Depression Inventory (MDI). The secondary outcomes are anxiety measured by a visual analogue scale (VAS), minutes of sleep, sleep effectiveness, sleep latency and periods awake measured by actigraphy and changes in cognitive function measured by a neuropsychological test-battery. Tertiary outcomes are fatigue, pain, well-being and sleep quality/quantity measured by VAS, sleep diary and sleepiness measured by the Karolinska Sleepiness Scale. The PER3 genotype is also to be determined in blood samples.

Ethics: The study is approved by the local ethics committee (H-4-2011-007). The study has also been approved by The Danish Medicines Agency (EudraCT nr. 2010-022460-12) and The Danish Data Protection Agency (2007-58-0015/HEH.750.89-12). The project is registered on www.clinicaltrials.gov - clinicaltrials.gov identifier: NCT01355523.

INTRODUCTION

Breast cancer is the most common type of cancer among women worldwide with about 1.4 million new cases every year¹. Breast cancer accounts for 31 % of the various cancer diagnoses in women and is responsible for 15 % of deaths in females due to cancer². For Danish women it is the most common type of cancer and the incidence is rising³. The incidence rises towards the age of 65 and then the curve flattens out³. Improvement of treatment has led to increasing 5 year-survival which is now 84 % in Denmark⁴ and 89 % in the US⁵. Now focus has turned to optimizing quality of life because these patients may have a number of different psychological and physical symptoms such as depression, anxiety, fatigue, cognitive dysfunction and sleep disturbances⁶⁻¹².

METHODS

Study design and objective

MELODY (The effect of MELatOnin on Depression, anxiety, cognitive function and sleep disturbances in breast cancer patients) is a prospective double-blinded, randomized, placebo-controlled trial in which we intend to include 260 patients undergoing surgery for breast cancer.

The objective is to investigate whether treatment with oral melatonin has a prophylactic or ameliorating effect on depressive symptoms, anxiety, sleep disturbances and cognitive dysfunction in women with breast cancer. Furthermore, we will examine whether a specific clock-gene PER3 is correlated with an increased risk of depressive symptoms, sleep disturbances or cognitive function. Patients in the intervention group will receive 6 mg oral melatonin daily 1 hour before bedtime for 1 week preoperatively to 12 weeks postoperatively. Patients in the control group will receive placebo.

Study population:

Table 1: Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
<ul style="list-style-type: none"> • Female between 30-75 years • Lumpectomy or mastectomy • American Society of Anesthesiologists (ASA) class I-III • No sign of depression on Major Depression Inventory (MDI) • Not pregnant 	<ul style="list-style-type: none"> • Neoadjuvant chemotherapy • Treatment with: <ul style="list-style-type: none"> - Selective serotonin reuptake inhibitors (SSRI) - Antithrombotic drug therapy (except 75 mg acetylsalicylic acid (ASA) daily) - Monoaminoxidase (MAO) inhibitors - Calcium channel blockers • Rotor or Dubin-Johnson syndrome • Epilepsy • Known allergic reaction to melatonin • Known and treated sleep apnea

	<ul style="list-style-type: none"> • Diabetes mellitus treated with insulin • Ongoing or previous medically treated depression or bipolar disorder • Known autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis or multiple sclerosis) • Incompensated liver cirrhosis • Severe kidney disease (receiving dialysis) • Previous or other current cancer • Known medically treated sleep disorder (insomnia, restless legs etc.) • Shift-work or night-work • Daily intake of more than 5 units (1 unit = 8 g pure alcohol) • Pre-operative, continuous treatment with psychopharmacological drugs of any kind, opioids, anxiolytics or hypnotics • Predicted bad compliance • Breast-feeding • Pre-operative Mini Mental State Evaluation (MMSE) score less than 24
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Approximately 1 week preoperatively patients are individually assessed and screened for inclusion. This includes a MMSE, a neuropsychological test with the ISPOCD test battery¹³ and the MDI¹⁴⁻¹⁶. Hereafter, patients will on a daily basis fill out visual analogue scales (VAS) regarding anxiety, fatigue, pain, general well-being and sleep, complete a sleep diary and fill out the Karolinska Sleepiness Scale (KSS). An Actigraph will be mounted on the wrist and worn continuously until two weeks postoperatively. Patients will be randomized to either 6 mg (2x3mg) melatonin or placebo. Patients will be instructed to take their medicine every evening at 9-10 p.m. and continue with this for 13 weeks. A blood sample will be collected for the analysis of PER3 genotype. A visit is scheduled 2 weeks postoperatively where patients are tested with the ISPOCD test battery and the MDI. At this time the Actigraph will be taken off. During the last 10 weeks of the study patients will be assessed with the MDI twice, and every two weeks fill out visual analogue scales (VAS) regarding anxiety, fatigue, pain, general well-being and sleep, complete a sleep diary and fill out the Karolinska Sleepiness Scale (KSS). At the final visit 12 weeks postoperatively patients will be tested with the ISPOCD test battery and the MDI.

Randomization

Patients who have provided written and informed consent preceding inclusion and who meet all the inclusion criteria and none of the exclusion criteria are randomized to either melatonin 6 mg or placebo. Inclusion and randomization is done 1 week preoperatively.

The randomization is based on blocks of 6. The randomization list is computer generated using dedicated software (www.randomization.com). To ensure that the randomization list is not known to the investigator this procedure is completed by the pharmacy who receives the medicine directly from Pharma Nord ApS, Vejle, Denmark. In case of drop-outs leading to less than 120 patients in

each group, the study will include new blocks of 6 patients to ensure randomization and balance between the two groups.

Melatonin

Melatonin is a hormone which is produced at night in the corpus pineale in a rhythmical pattern, controlled by an endogenous clock in the suprachiasmatic nucleus of the hypothalamus¹⁷. Its main function is to synchronize the circadian rhythm¹⁷. Melatonin is mostly known for its role as a circadian hormone but it also has known sedative^{18;19}, anxiolytic^{18;19}, analgesic^{20;21}, antihypertensive^{22;23}, non-inflammatory²⁴ and oncostatic effects²⁵⁻²⁷. Melatonin has a possible antidepressive effect²⁸⁻³⁴ probably based on its effect on the central circadian regulation³⁵ and an effect on improving cognitive function³⁶. Figure 1 shows the complexity of the relationship between breast cancer and depression and the possible attack points of melatonin.

The secretion rhythm, fluctuations and levels of melatonin have been previously investigated with regards to surgery, depression and also breast cancer. After surgery melatonin secretion has shown to be acutely disturbed³⁷ with a delay of secretion and reduced amplitude^{38;39}. Various lines of evidence show that depressed patients exhibit disturbances in both the amplitude and the shape of the melatonin secretion rhythm, with some studies showing a low nocturnal melatonin secretion and others showing an increase in secretion³⁵. A growing amount of evidence from prospective studies suggest an association between night work and breast cancer risk, most likely due to subsequent melatonin suppression⁴⁰.

Melatonin is relatively non-toxic⁴¹⁻⁴³. Animal studies have shown that the maximum dose given in vivo, without any adverse effects or death is 200 mg/kg for pregnant rats throughout the whole pregnancy and 800 mg/kg for mice^{44;45}. The drug has been used in many clinical studies of both adults^{18-20;22;41;42;46;47} and newborns^{48;49} without serious adverse effects. Doses of 1000 mg daily for one month have been given and the only reported adverse effect was drowsiness⁴¹. In a recent systematic review the most often reported side effects were headache, dizziness, nausea and drowsiness⁵⁰.

PER3 clock-gene

Previous studies have shown that certain genes, called clock-genes, have a role in regulating circadian rhythms and sleep in humans⁵¹. A coding region in the clock-gene PER3, which is repeated in either 4 or 5 units has been coupled to various phenotypical traits; A or B people, sleep diseases⁵²⁻⁵⁴, affective disorders^{55;56}, cognitive function after sleep deprivation^{54;57} and in one

study⁵⁸ a relationship was found between the 5/5 or 4/5 genotype of the PER3 gene and breast cancer. We would like to investigate whether sleep quality, cognitive function or depressive symptoms are correlated with any of these three PER3 genotypes.

Ethics

The study will be performed in agreement with the Helsinki II declaration and law 503 of 1992 about the Scientific Ethics Committee System and is approved by the local ethics committee (H-4-2011-007). The study has also been approved by The Danish Medicines Agency (EudraCT nr. 2010-022460-12) and The Danish Data Protection Agency (2007-58-0015/HEH.750.89-12). The project is registered on www.clinicaltrials.gov as recommended by the International Committee of Medical Journal Editors - clinicaltrials.gov identifier: NCT01355523.

EFFECT PARAMETERS

Table 2: Effect parameters

PRIMARY EFFECT PARAMETER	SECONDARY EFFECT PARAMETERS	TERTIARY EFFECT PARAMETERS
<ul style="list-style-type: none"> MDI (Major Depression Inventory) 	<ul style="list-style-type: none"> Anxiety measured by VAS Minutes of sleep, sleep efficiency, sleep latency and periods awake measured by actigraphy Changes in cognitive function measured by a neuropsychological test-battery PER3 genotype correlated with sleep, cognitive function and depressive symptoms 	<ul style="list-style-type: none"> Fatigue, pain, well-being and sleep quality/quantity measured by VAS Sleep diary Sleepiness measured by the Karolinska Sleepiness Scale

Major Depression Inventory (MDI)

Major Depression Inventory is a self-rating scale including 12 questions. The questionnaire is already well documented in a Danish population¹⁴. The questions cover the 10 ICD-10 questions for depression and the symptoms are identical with the DSM-IV major depression diagnosis apart from one symptom, low self esteem (question 4), which in DSM-IV is incorporated in the question about guilt (question 5). The MDI includes 10 items, where item 8 and 10 are divided into two sub-questions a and b. For item 8 and 10 the highest score of question a and b is included. The individual items are measured on a 6-point Likert scale with graduations depending on the extent of the symptom the last 14 days; 0 (the symptom has not been present) till 5 (the symptom has been present continuously).

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4 The MDI has a dual function. It can be used as a diagnostic tool where it can, by algorithms, lead to
5 either DSM-IV or ICD-10 categories of “major” or “moderate to severe depression”. An acceptable
6 sensitivity and specificity for the diagnosis of depression according to ICD-10 and DSM-III/DSM-
7 IV has previously been found¹⁵. The MDI can also be used as a measuring instrument to indicate
8 the severity of the depression. Thus, the MDI correlates with the Hamiltons Depressions Scale
9 (HAM-D)¹⁶.

14 **Actigraphy**

15 Actigraphy is a well known non-invasive method to objectively measure sleep. Using an Actigraph,
16 activity levels are registered by a wrist-worn mini-computer. This method which does not disturb
17 the patients’ sleep has been used for many years⁵⁹ and also in the postoperative setting⁶⁰. It has
18 been shown that actigraphy has a high sensitivity and specificity for detecting sleep start, sleep
19 periods and awakenings⁵⁹.

20 An actigraph measures small accelerations with a piezo-electrode and stores this in a memory. Data
21 can be recorded via different modalities and we will be using the zero crossing method, where all
22 accelerations (> 0.1G) which cross a certain threshold (0 or very close to 0) will be detected. The
23 sleep analysis will be performed by dedicated software (Action4 software, Ambulatory Monitoring
24 Inc., NY, USA) by using the Cole-Kripke algorithm⁶¹. Data will be reported as total sleep time per
25 period, sleep efficiency, sleep ratio, number of awakenings and duration of awakenings. The
26 method is validated and has been used previously to measure sleep in patients with breast cancer
27 before, during and after surgery⁶²⁻⁶⁵.

38 **The ISPOCD neuropsychological test battery**

39 The cognitive function of the patients will be tested preoperatively and at 2 weeks and 3 months
40 postoperatively. The test battery consists of 4 validated tests: the Visual Verbal Learning Test, the
41 Stroop Colour-Word Test, the Letter-Digit Coding Test and the Concept Shifting Task.

42 The test battery takes approximately 45 minutes to complete and has been used previously in the
43 large multicenter ISPOCD trial¹³.

50 **Anxiety and sleep quality measurements**

51 A subjective feeling of anxiety will be registered on a VAS going from “no anxiety” to “worst
52 possible anxiety”. Measurements will take place daily for the first three weeks of the study and
53 every two weeks for the last 10 weeks.
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4 Subjective sleep quality will be registered on a VAS going from “best possible sleep” equivalent to
5 0 mm to “worst possible sleep” equivalent to 100 mm. Patients will also fill out VAS regarding
6 general well-being, fatigue and pain. Measurements will take place at the same time as for anxiety.
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8 Furthermore, a sleep diary recording sleep time and awakening time, will be completed daily for the
9 first 3 weeks of the study and thereafter every 14 days. Patients will at the same time periods
10 complete the KSS which is used to quantify levels of sleepiness. KSS is a 9 point scale from 1 (very
11 awake) to 9 (very sleepy), where a score of 7 or more reflects pathological sleepiness⁶⁶.
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16 17 **Other collected data**

18 Age, weight, height, menopausal status, educational level, cohabitation status, work market
19 affiliation, household income, number of children/number of children living at home, smoking
20 habits, ASA class, duration of surgery, the size of the incision, consumption of analgesics
21 postoperatively and which postoperative oncological treatment each patient receives after surgery.
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26 27 **STATISTICAL ANALYSIS AND SAMPLE SIZE CALCULATION**

28 The sample size estimation is based on a conservative estimate of the incidence of depression of
29 30% in breast cancer patients⁷ with a reduction to 15% with melatonin treatment. With a power of
30 80%, a risk of type I error of 5% and a risk of type II error of 20% we should include 120 patients in
31 each group receiving melatonin or placebo. We have chosen to include 130 patients in each group.
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33 Statistical analyses will be done using SPSS Version 18.0.
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36 Regarding our primary outcome mean MDI total scores and prevalences of ICD-10 mild, moderate
37 and severe depression will be calculated for both samples. Normality of the data will be tested by
38 one sample Kolmogorov-Smirnov test and parametric or non-parametric statistics will be used
39 accordingly. The two groups will be compared by Fisher’s exact test for the primary outcome.
40 Paired Student’s t-test or Wilcoxon test will be used for intra-group comparisons and unpaired
41 Student’s t-test or Mann-Whitney’s test for inter-group comparisons. For repeated measures
42 Friedman test or an ANOVA will be used when appropriate.
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48 For comparing anxiety by VAS and sleep architecture (objective data from the Actigraph) we will
49 do inter-group comparisons with Mann-Whitney’s test and intra-group comparisons using the
50 Wilcoxon signed rank test.
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53 For analyzing POCD in the two groups we will use 2x2 tables and a Fisher’s exact test. Patients will
54 be defined as having POCD if 2 of the seven Z-scores in individual test or the combined Z-score are
55 1.96 or more¹³. ANOVA will be used to analyze the 2 groups and the specific Z-scores for the
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4 seven subtests and the combined Z-scores. A Bonferroni correction will be made when performing
5 multiple comparisons.
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7 For analyses of correlation between PER3 genotype and sleep, cognitive function and depressive
8 symptoms a logistic regression analysis will be used. For the subjective parameters fatigue, pain,
9 general wellbeing and sleep quality/quantity measured by VAS and sleepiness by KSS we will do
10 inter-group comparisons with the Mann Whitney test and intra-group comparisons using the
11 Wilcoxon signed rank test. We plan to do intention-to-treat as well as per protocol analyses. In
12 general, $p < 0.05$ will be considered statistically significant.
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17 18 19 **DISCUSSION**

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21 There is a complex relationship between depression and breast cancer with influence from various
22 factors – figure 1. Due to the high frequencies of depression, anxiety, sleep disturbances and
23 cognitive dysfunction in patients with breast cancer, a high interest is found in preventing these co-
24 morbid symptoms.
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27 Depression is both underdiagnosed and undertreated in many cancer patients^{11;67}, especially those
28 with breast cancer⁶⁸. The overall rate of depression in patients with breast cancer is higher than in
29 most cancers. This is most likely because menopause, either naturally occurring or premature due to
30 the effects of chemotherapy and/or anti-hormone treatment, and estrogen decline are related to
31 depression⁶. It has been shown that up to 50 % of patients with breast cancer may experience
32 depression and/or anxiety within the first year of diagnosis⁷. Concomitant breast cancer and
33 depression is associated with higher mortality and morbidity^{67;69-72} but also lower patient
34 satisfaction⁷³ and compliance to adjuvant therapy⁷⁴ and general medical treatment⁷⁵. Even a year
35 after surgery many women still deal with an anxiety problem⁷⁶ and about 15 % are still depressed⁷.
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37 Studies have shown that treating anxiety and depression in these patients with breast cancer
38 improves their quality of life, leads to a higher completion of adjuvant therapy and extends their
39 lifetime^{68;77;78}. Therefore it is important to optimize the treatment of these symptoms.
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47 A number of randomized controlled trials have examined the efficacy of antidepressants compared
48 with placebo in patients with breast cancer⁷⁸⁻⁸⁵. A high number of drop-outs due to side effects
49 related to the antidepressant treatment have also rendered such trials difficult to complete^{79;84;86}.
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51 Furthermore, recent evidence indicates that some selective serotonin reuptake inhibitor
52 antidepressants may reduce tamoxifen's effectiveness and are associated with an increased risk of
53 mortality^{87;88}.
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4 Sleep disturbances are a frequent problem in cancer patients^{89;90}. Compared with other types of
5 cancer breast cancer is associated with an exceptionally high rate of reduced sleep quality^{10;89}
6 which can be found even many years after end of treatment⁸. The estimated prevalence of sleep
7 problems among patients with breast cancer is between 38-61%^{10;89;91;92}, and it may reduce quality
8 of life in this group of patients^{91;93}. About 30 % of patients with breast cancer take hypnotics^{10;89;92}
9 leading to a potential dependency problem and it is therefore important to focus on treatments with
10 less adverse effects.
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12 The sleep disturbances can be due to a variety of factors, both physical and psychological, which all
13 have a mutual influence on each other. Among the psychological factors, depression and anxiety are
14 well-known and these patients also exhibit a change in sleep architecture⁹⁴. In general, depressed
15 patients display sleep abnormalities such as difficulties falling asleep and staying asleep, loss of
16 slow-wave-sleep and changed REM sleep⁹⁵. Pain and hot flushes are examples of the physical
17 factors^{8;91;92}.

18 Overall, it is difficult to conclude whether sleep disturbances are a precursor or a sequelae of
19 depression. Various studies in healthy individuals have shown a causal relationship between sleep
20 disturbances and the following development of depression^{96;97}. More specifically for patients with
21 breast cancer, a circadian rhythm disruption has been associated with depression, fatigue and pain
22 ^{62;63;65;98}. Altogether there is a complicated relationship between circadian disturbances, sleep and
23 mood³⁵ and this is especially prevalent in patients with breast cancer⁹⁹.

24 Disturbances of cognitive function are a prevalent phenomenon in patients with breast cancer and
25 can influence the general quality of life in this group of patients^{9;12}. Studies have suggested that the
26 cancer *per se* and/or the treatment with surgery, radiation, chemotherapy and hormone therapy or
27 genetics can be contributing factors in the development of cognitive disturbances^{100;101}. POCD
28 (postoperative cognitive dysfunction) is characterized by a deterioration in memory, concentration
29 and information assessment after surgery¹³.

30 In other settings some studies have shown that melatonin can attenuate cognitive dysfunction
31 ^{36;102;103} and this mechanism together with the general improvement of sleep could be beneficial on
32 cognitive disturbances in this specific group of patients. Since there is no specific knowledge on this
33 topic with regards to breast cancer it is necessary to investigate whether the development of
34 cognitive problems can be prevented by melatonin treatment.
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4 In conclusion we hope, with this project, to decrease the occurrence of depression, anxiety, sleep
5 disturbances and cognitive dysfunction in patients with breast cancer and in a larger perspective
6 reduce morbidity and mortality and improve quality of life for these patients. With regards to
7 genetics this project could lead to the possibility of being able to detect women with a higher risk of
8 developing the abovementioned problems and then give indication for selective prophylactic
9 treatment. The diversity of melatonin's physiological functions and treatment effects are
10 continuously being investigated in both animal and human studies. To-date, the effect of melatonin
11 in a breast cancer population with the above-mentioned indications has not yet been studied.
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19 Conflict of interest statement:

20 No conflicts of interest.
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24 Funding statement:

25 This work was supported by grants from the University of Copenhagen, The Aase and Ejnar
26 Danielsens Foundation, The A.P.Møller Foundation for the Advancement of Medical Science, The
27 Else and Mogens Wedell Wedellborgs Foundation, The Beckett Foundation, The Hede Nielsen
28 Family Foundation, The Dagmar Marshalls Foundation and Manufacturer Einar Willumsen's
29 Memorial Scholarship. Pharma Nord provided the melatonin and placebo tablets but had no
30 influence on the study design and will have no influence on the interpretation of results.
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57
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59
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Reference List

- (1) <http://globocan.iarc.fr/factsheets/cancers/breast.asp> (accessed November 2011).
- (2) Greenlee RT, Hill-Harmon MB, Murray T et al. . Cancer statistics, 2001. *CA Cancer J Clin* 2001;**51**:15-36.
- (3) http://www.sst.dk/publ/Publ2009/DOKU/cancerreg/cancerregisteret_2008.pdf (accessed November 2011).
- (4) <http://www.sst.dk/publ/Publ2010/DOKU/SygehusbaseretOverlevelse/SygehuspatientersOverlevelse1997-2008.pdf> (accessed November 2011).
- (5) <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-030975.pdf> (accessed November 2011).
- (6) Fann JR, Thomas-Rich AM, Katon WJ et al. Major depression after breast cancer: a review of epidemiology and treatment. *Gen Hosp Psychiatry* 2008;**30**:112-126.
- (7) Burgess C, Cornelius V, Love S et al. Depression and anxiety in women with early breast cancer: five year observational cohort study. *BMJ* 2005;**330**:702-705.

- 1
2
3
4 (8) Otte JL, Carpenter JS, Russell KM et al. Prevalence, Severity, and Correlates of Sleep-Wake
5 Disturbances in Long-Term Breast Cancer Survivors. *J Pain Symptom Manage*
6 2010;**39**:535-547.
7
8
9
10
11 (9) Debess J, Riis JO, Pedersen L et al. Cognitive function and quality of life after surgery for
12 early breast cancer in North Jutland, Denmark. *Acta Oncol* 2009;**48**:532-540.
13
14
15
16
17 (10) Savard J, Simard S, Blanchet J et al. Prevalence, clinical characteristics, and risk factors for
18 insomnia in the context of breast cancer. *Sleep* 2001;**24**:583-590.
19
20
21
22 (11) Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr*
23 2004;**32**:57-71.
24
25
26
27
28 (12) Schou I, Ekeberg O, Sandvik L et al. Multiple predictors of health-related quality of life in
29 early stage breast cancer. Data from a year follow-up study compared with the general
30 population. *Qual Life Res* 2005;**14**:1813-1823.
31
32
33
34
35 (13) Moller JT, Cluitmans P, Rasmussen LS et al. Long-term postoperative cognitive dysfunction
36 in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative
37 Cognitive Dysfunction. *Lancet* 1998;**351**:857-861.
38
39
40
41
42
43 (14) Olsen LR, Mortensen EL, Bech P. Prevalence of major depression and stress indicators in
44 the Danish general population. *Acta Psychiatr Scand* 2004;**109**:96-103.
45
46
47
48 (15) Bech P, Rasmussen NA, Olsen LR et al. The sensitivity and specificity of the Major
49 Depression Inventory, using the Present State Examination as the index of diagnostic
50 validity. *J Affect Disord* 2001;**66**:159-164.
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (16) Olsen LR, Jensen DV, Noerholm V et al. The internal and external validity of the Major
5
6 Depression Inventory in measuring severity of depressive states. *Psychol Med* 2003;**33**:351-
7
8 356.
9
- 10
11 (17) Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin.
12
13 *Sleep Med Rev* 2005;**9**:11-24.
14
15
- 16
17 (18) Acil M, Basgul E, Celiker V et al. Perioperative effects of melatonin and midazolam
18
19 premedication on sedation, orientation, anxiety scores and psychomotor performance. *Eur J*
20
21 *Anaesthesiol* 2004;**21**:553-557.
22
23
- 24
25 (19) Naguib M, Samarkandi AH. Premedication with melatonin: a double-blind, placebo-
26
27 controlled comparison with midazolam. *Br J Anaesth* 1999;**82**:875-880.
28
29
- 30
31 (20) Caumo W, Torres F, Moreira NL, Jr. et al. The clinical impact of preoperative melatonin on
32
33 postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg*
34
35 2007;**105**:1263-71.
36
37
- 38
39 (21) Srinivasan V, Pandi-Perumal SR, Spence DW et al. Potential use of melatonergic drugs in
40
41 analgesia: mechanisms of action. *Brain Res Bull* 2010;**81**:362-371.
42
43
- 44
45 (22) Cagnacci A, Cannoletta M, Renzi A et al. Prolonged melatonin administration decreases
46
47 nocturnal blood pressure in women. *Am J Hypertens* 2005;**18**:1614-1618.
48
49
- 50
51 (23) Kitajima T, Kanbayashi T, Saitoh Y et al. The effects of oral melatonin on the autonomic
52
53 function in healthy subjects. *Psychiatry Clin Neurosci* 2001;**55**:299-300.
54
55
- 56
57 (24) Maestroni GJ. The immunotherapeutic potential of melatonin. *Expert Opin Investig Drugs*
58
59 2001;**10**:467-476.
60

- 1
2
3
4 (25) Vijayalaxmi, Thomas CR, Jr., Reiter RJ et al. Melatonin: from basic research to cancer
5 treatment clinics. *J Clin Oncol* 2002;**20**:2575-2601.
6
7
8
9 (26) Reiter RJ. Mechanisms of cancer inhibition by melatonin. *J Pineal Res* 2004;**37**:213-214.
10
11
12 (27) Grant SG, Melan MA, Latimer JJ et al. Melatonin and breast cancer: cellular mechanisms,
13 clinical studies and future perspectives. *Expert Rev Mol Med* 2009;**11**:e5.
14
15
16
17 (28) Bellipanni G, Di MF, Blasi F, Di MA. Effects of melatonin in perimenopausal and
18 menopausal women: our personal experience. *Ann N Y Acad Sci* 2005;**1057**:393-402.
19
20
21
22 (29) Kopp C, Vogel E, Rettori MC et al. The effects of melatonin on the behavioural
23 disturbances induced by chronic mild stress in C3H/He mice. *Behav Pharmacol* 1999;**10**:73-
24 83.
25
26
27
28
29
30 (30) Hickie IB, Rogers NL. Novel melatonin-based therapies: potential advances in the treatment
31 of major depression. *Lancet* 2011;**378**:621-631.
32
33
34
35
36 (31) Serfaty MA, Osborne D, Buszewicz MJ et al. A randomized double-blind placebo-
37 controlled trial of treatment as usual plus exogenous slow-release melatonin (6 mg) or
38 placebo for sleep disturbance and depressed mood. *Int Clin Psychopharmacol* 2010;**25**:132-
39 142.
40
41
42
43
44
45 (32) Spadoni G, Bedini A, Rivara S et al. Melatonin Receptor Agonists: New Options for
46 Insomnia and Depression Treatment. *CNS Neurosci Ther* Published Online First: 15 October
47 2010. doi: 10.1111/j.1755-5949.2010.00197
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (33) Garzon C, Guerrero JM, Aramburu O et al. Effect of melatonin administration on sleep,
5 behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-
6 blind, placebo-controlled study. *Aging Clin Exp Res* 2009;**21**:38-42.
7
8
9
10
11 (34) Rahman SA, Kayumov L, Shapiro CM. Antidepressant action of melatonin in the treatment
12 of Delayed Sleep Phase Syndrome. *Sleep Med* 2010;**11**:131-136.
13
14
15
16
17 (35) Srinivasan V, Pandi-Perumal SR, Trakht I et al. Pathophysiology of depression: role of sleep
18 and the melatonergic system. *Psychiatry Res* 2009;**165**:201-214.
19
20
21
22 (36) Furio AM, Brusco LI, Cardinali DP. Possible therapeutic value of melatonin in mild
23 cognitive impairment: a retrospective study. *J Pineal Res* 2007;**43**:404-409.
24
25
26
27
28 (37) Ram E, Vishne TH, Weinstein T et al. General anesthesia for surgery influences melatonin
29 and cortisol levels. *World J Surg* 2005;**29**:826-829.
30
31
32
33 (38) Karkela J, Vakkuri O, Kaukinen S et al. The influence of anaesthesia and surgery on the
34 circadian rhythm of melatonin. *Acta Anaesthesiol Scand* 2002;**46**:30-36.
35
36
37
38 (39) Gogenur I, Middleton B, Kristiansen VB et al. Disturbances in melatonin and core body
39 temperature circadian rhythms after minimal invasive surgery. *Acta Anaesthesiol Scand*
40 2007;**51**:1099-1106.
41
42
43
44
45
46 (40) Megdal SP, Kroenke CH, Laden F et al. Night work and breast cancer risk: a systematic
47 review and meta-analysis. *Eur J Cancer* 2005;**41**:2023-2032.
48
49
50
51 (41) Nordlund JJ, Lerner AB. The effects of oral melatonin on skin color and on the release of
52 pituitary hormones. *J Clin Endocrinol Metab* 1977;**45**:768-774.
53
54
55
56
57
58
59
60

- 1
2
3
4 (42) Nickkholgh A, Schneider H, Sobirey M et al. The use of high-dose melatonin in liver
5 resection is safe: first clinical experience. *J Pineal Res* 2011;**50**:381-388.
6
7
8
9
10 (43) Seabra ML, Bignotto M, Pinto LR, Jr. et al. Randomized, double-blind clinical trial,
11 controlled with placebo, of the toxicology of chronic melatonin treatment. *J Pineal Res*
12 2000;**29**:193-200.
13
14
15
16
17 (44) Jahnke G, Marr M, Myers C et al. Maternal and developmental toxicity evaluation of
18 melatonin administered orally to pregnant Sprague-Dawley rats. *Toxicol Sci* 1999;**50**:271-
19 279.
20
21
22
23
24 (45) Barchas J, DaCosta F, Spector S. Acute pharmacology of melatonin. *Nature* 1967;**214**:919-
25 920.
26
27
28
29
30 (46) Shaw KM, Stern GM, Sandler M. Melatonin and parkinsonism. *Lancet* 1973;**1**:271.
31
32
33 (47) Zhdanova IV, Wurtman RJ, Morabito C et al. Effects of low oral doses of melatonin, given
34 2-4 hours before habitual bedtime, on sleep in normal young humans. *Sleep* 1996;**19**:423-
35 431.
36
37
38
39
40 (48) Gitto E, Romeo C, Reiter RJ et al. Melatonin reduces oxidative stress in surgical neonates. *J*
41 *Pediatr Surg* 2004;**39**:184-189.
42
43
44
45
46 (49) Gitto E, Karbownik M, Reiter RJ et al. Effects of melatonin treatment in septic newborns.
47 *Pediatr Res* 2001;**50**:756-760.
48
49
50
51 (50) Buscemi N, Vandermeer B, Hooton N et al. Efficacy and safety of exogenous melatonin for
52 secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis.
53 *BMJ* 2006;**332**:385-393.
54
55
56
57
58
59
60

- 1
2
3
4 (51) Dijk DJ, Archer SN. PERIOD3, circadian phenotypes, and sleep homeostasis. *Sleep Med*
5 *Rev* 2010;**14**:151-160.
6
7
8
9 (52) Archer SN, Robilliard DL, Skene DJ et al. A length polymorphism in the circadian clock
10 gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep*
11 2003;**26**:413-415.
12
13
14
15 (53) Johansson C, Willeit M, Smedh C et al. Circadian clock-related polymorphisms in seasonal
16 affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology*
17 2003;**28**:734-739.
18
19
20
21
22 (54) Viola AU, Archer SN, James LM et al. PER3 polymorphism predicts sleep structure and
23 waking performance. *Curr Biol* 2007;**17**:613-618.
24
25
26
27
28 (55) Nievergelt CM, Kripke DF, Barrett TB et al. Suggestive evidence for association of the
29 circadian genes PERIOD3 and ARNTL with bipolar disorder. *Am J Med Genet B*
30 *Neuropsychiatr Genet* 2006;**141B**:234-241.
31
32
33
34 (56) Artioli P, Lorenzi C, Pirovano A et al. How do genes exert their role? Period 3 gene variants
35 and possible influences on mood disorder phenotypes. *Eur Neuropsychopharmacol*
36 2007;**17**:587-594.
37
38
39
40 (57) Groeger JA, Viola AU, Lo JC et al. Early morning executive functioning during sleep
41 deprivation is compromised by a PERIOD3 polymorphism. *Sleep* 2008;**31**:1159-1167.
42
43
44
45 (58) Zhu Y, Brown HN, Zhang Y et al. Period3 structural variation: a circadian biomarker
46 associated with breast cancer in young women. *Cancer Epidemiol Biomarkers Prev*
47 2005;**14**:268-270.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (59) Ancoli-Israel S, Cole R, Alessi C et al. The role of actigraphy in the study of sleep and
5 circadian rhythms. *Sleep* 2003;**26**:342-392.
6
7
8
9 (60) Bisgaard T, Kjaersgaard M, Bernhard A et al. Computerized monitoring of physical activity
10 and sleep in postoperative abdominal surgery patients. *J Clin Monit Comput* 1999;**15**:1-8.
11
12
13 (61) Cole RJ, Kripke DF, Gruen W et al. Automatic sleep/wake identification from wrist activity.
14 *Sleep* 1992;**15**:461-469.
15
16
17 (62) Berger AM, Wielgus K, Hertzog M et al. Patterns of circadian activity rhythms and their
18 relationships with fatigue and anxiety/depression in women treated with breast cancer
19 adjuvant chemotherapy. *Support Care Cancer* 2010;**18**:105-114.
20
21
22 (63) Wright CE, Bovbjerg DH, Montgomery GH et al. Disrupted sleep the night before breast
23 surgery is associated with increased postoperative pain. *J Pain Symptom Manage*
24 2009;**37**:352-362.
25
26
27 (64) Ancoli-Israel S, Liu L, Marler MR et al. Fatigue, sleep, and circadian rhythms prior to
28 chemotherapy for breast cancer. *Support Care Cancer* 2006;**14**:201-209.
29
30
31 (65) Roscoe JA, Morrow GR, Hickok JT et al. Temporal interrelationships among fatigue,
32 circadian rhythm and depression in breast cancer patients undergoing chemotherapy
33 treatment. *Support Care Cancer* 2002;**10**:329-336.
34
35
36 (66) Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J*
37 *Neurosci* 1990;**52**:29-37.
38
39
40 (67) Caplette-Gingras A, Savard J. Depression in women with metastatic breast cancer: a review
41 of the literature. *Palliat Support Care* 2008;**6**:377-387.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (68) Somerset W, Stout SC, Miller AH et al. Breast cancer and depression. *Oncology*
5 2004;**18**:1021-1034.
6
7
8
9 (69) Hjerl K, Andersen EW, Keiding N et al. Depression as a prognostic factor for breast cancer
10 mortality. *Psychosomatics* 2003;**44**:24-30.
11
12
13 (70) Watson M, Haviland JS, Greer S et al. Influence of psychological response on survival in
14 breast cancer: a population-based cohort study. *Lancet* 1999;**354**:1331-1336.
15
16
17 (71) Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and
18 mortality in cancer patients: a meta-analysis. *Cancer* 2009;**115**:5349-5361.
19
20
21 (72) Abrams TE, Vaughan-Sarrazin M, Rosenthal GE. Influence of psychiatric comorbidity on
22 surgical mortality. *Arch Surg* 2010;**145**:947-953.
23
24
25 (73) Bui QU, Ostir GV, Kuo YF et al. Relationship of depression to patient satisfaction: findings
26 from the barriers to breast cancer study. *Breast Cancer Res Treat* 2005;**89**:23-28.
27
28
29 (74) Colleoni M, Mandala M, Peruzzotti G et al. Depression and degree of acceptance of
30 adjuvant cytotoxic drugs. *Lancet* 2000;**356**:1326-1327.
31
32
33 (75) DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with
34 medical treatment: meta-analysis of the effects of anxiety and depression on patient
35 adherence. *Arch Intern Med* 2000;**160**:2101-2107.
36
37
38 (76) Hartl K, Schennach R, Muller M et al. Quality of life, anxiety, and oncological factors: a
39 follow-up study of breast cancer patients. *Psychosomatics* 2010;**51**:112-123.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (77) Giese-Davis J, Collie K, Rancourt KM et al. Decrease in depression symptoms is associated
5
6 with longer survival in patients with metastatic breast cancer: a secondary analysis. *J Clin*
7
8 *Oncol* 2011;**29**:413-420.
9
- 10
11 (78) Navari RM, Brenner MC, Wilson MN. Treatment of depressive symptoms in patients with
12
13 early stage breast cancer undergoing adjuvant therapy. *Breast Cancer Res Treat*
14
15 2008;**112**:197-201.
16
17
- 18
19 (79) Pezzella G, Moslinger-Gehmayr R, Contu A. Treatment of depression in patients with breast
20
21 cancer: a comparison between paroxetine and amitriptyline. *Breast Cancer Res Treat*
22
23 2001;**70**:1-10.
24
25
- 26
27 (80) Roscoe JA, Morrow GR, Hickok JT et al. Effect of paroxetine hydrochloride (Paxil) on
28
29 fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res*
30
31 *Treat* 2005;**89**:243-249.
32
33
- 34
35 (81) van HK, Zivkov M. Pharmacological treatment of depression in cancer patients. A placebo-
36
37 controlled study of mianserin. *Br J Psychiatry* 1996;**169**:440-443.
38
39
- 40
41 (82) Musselman DL, Somerset WI, Guo Y et al. A double-blind, multicenter, parallel-group
42
43 study of paroxetine, desipramine, or placebo in breast cancer patients (stages I, II, III, and
44
45 IV) with major depression. *J Clin Psychiatry* 2006;**67**:288-296.
46
47
- 48 (83) Grassi L, Biancosino B, Marmai L et al. Effect of reboxetine on major depressive disorder in
49
50 breast cancer patients: an open-label study. *J Clin Psychiatry* 2004;**65**:515-520.
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (84) Fisch MJ, Loehrer PJ, Kristeller J et al. Fluoxetine versus placebo in advanced cancer
5
6 outpatients: a double-blinded trial of the Hoosier Oncology Group. *J Clin Oncol*
7
8 2003;**21**:1937-1943.
9
10
11 (85) Morrow GR, Hickok JT, Roscoe JA et al. Differential effects of paroxetine on fatigue and
12
13 depression: a randomized, double-blind trial from the University of Rochester Cancer Center
14
15 Community Clinical Oncology Program. *J Clin Oncol* 2003;**21**:4635-4641.
16
17
18 (86) Pirl WF, Roth AJ. Diagnosis and treatment of depression in cancer patients. *Oncology*
19
20 1999;**13**:1293-1301.
21
22
23 (87) Kelly CM, Juurlink DN, Gomes T et al. Selective serotonin reuptake inhibitors and breast
24
25 cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ*
26
27 2010;**340**:c693.
28
29
30 (88) Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via
31
32 cytochrome P450 2D6. *J Clin Psychiatry* 2009;**70**:1688-1697.
33
34
35 (89) Davidson JR, MacLean AW, Brundage MD et al. Sleep disturbance in cancer patients. *Soc*
36
37 *Sci Med* 2002;**54**:1309-1321.
38
39
40 (90) Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J*
41
42 *Clin Oncol* 2001;**19**:895-908.
43
44
45 (91) Fortner BV, Stepanski EJ, Wang SC et al. Sleep and quality of life in breast cancer patients.
46
47 *J Pain Symptom Manage* 2002;**24**:471-480.
48
49
50 (92) Koopman C, Nouriani B, Erickson V et al. Sleep disturbances in women with metastatic
51
52 breast cancer. *Breast J* 2002;**8**:362-370.
53
54
55
56
57
58
59
60

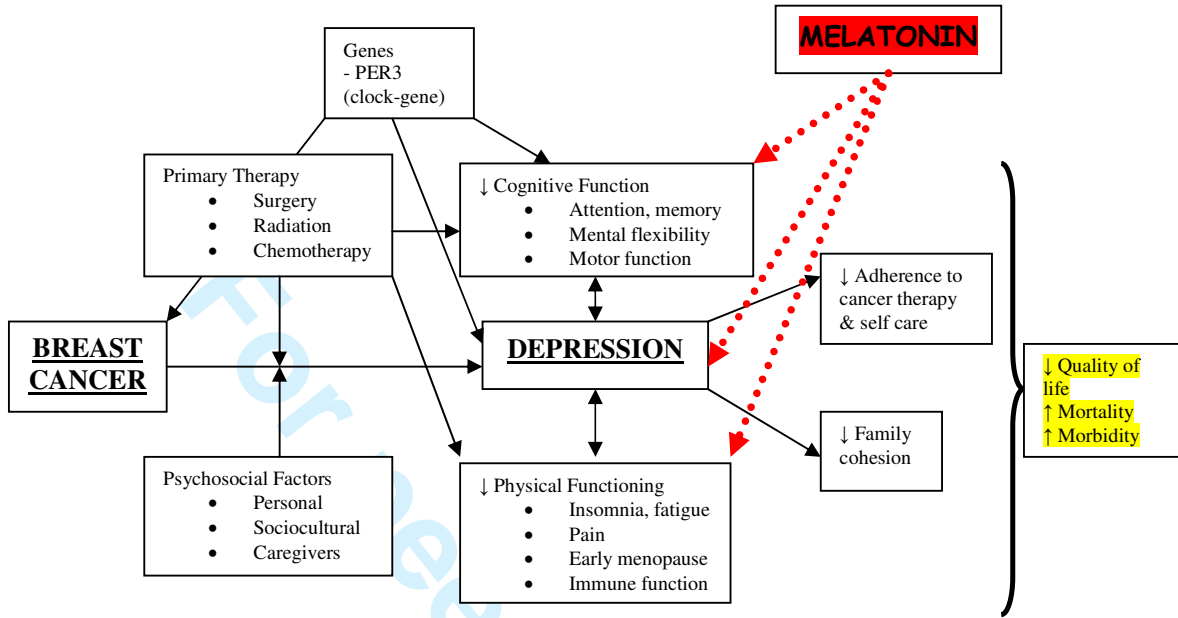
- 1
2
3
4 (93) Dow KH, Ferrell BR, Leigh S et al. An evaluation of the quality of life among long-term
5 survivors of breast cancer. *Breast Cancer Res Treat* 1996;**39**:261-273.
6
7
8
9 (94) Morin CM, Ware JC. Sleep and psychopathology. *Appl Prev Psychol* 1996;**5**:211-224.
10
11
12 (95) Benca RM, Okawa M, Uchiyama M et al. Sleep and mood disorders. *Sleep Med Rev*
13 1997;**1**:45-56.
14
15
16
17 (96) Breslau N, Roth T, Rosenthal L et al. Sleep disturbance and psychiatric disorders: a
18 longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;**39**:411-418.
19
20
21
22 (97) Livingston G, Blizzard B, Mann A. Does sleep disturbance predict depression in elderly
23 people? A study in inner London. *Br J Gen Pract* 1993;**43**:445-448.
24
25
26
27 (98) Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer
28 patients: a review. *Eur J Cancer Care (Engl)* 2001;**10**:245-255.
29
30
31
32 (99) Palesh OG, Collie K, Batiuchok D et al. A longitudinal study of depression, pain, and stress
33 as predictors of sleep disturbance among women with metastatic breast cancer. *Biol Psychol*
34 2007;**75**:37-44.
35
36
37
38 (100) Wefel JS, Lenzi R, Theriault R et al. 'Chemobrain' in breast carcinoma?: a prologue. *Cancer*
39 2004;**101**:466-475.
40
41
42
43 (101) Jim HS, Donovan KA, Small BJ et al. Cognitive functioning in breast cancer survivors: a
44 controlled comparison. *Cancer* 2009;**115**:1776-1783.
45
46
47
48 (102) Manda K, Reiter RJ. Melatonin maintains adult hippocampal neurogenesis and cognitive
49 functions after irradiation. *Prog Neurobiol* 2010;**90**:60-68.
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 (103) Sharma AK, Mehta AK, Rathor N et al. Melatonin attenuates cognitive dysfunction and
5
6 reduces neural oxidative stress induced by phosphamidon. *Fundam Clin Pharmacol*
7

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9 Published Online First: 26 July 2011. doi: 10.1111/j.1472-8206.2011.00977.x
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For peer review only

Figure 1: The relationship between breast cancer and depression



Modified after Fann JR et al. 2008⁶

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3-4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	3-4
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3-4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4,6-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	8-8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			4-5
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4-5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4-5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4-5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	3

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	4-5
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	4-5
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	
13		14b Why the trial ended or was stopped	
14			
15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
17		by original assigned groups	
18			
19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
20	estimation	precision (such as 95% confidence interval)	
21		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
22	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	
23		pre-specified from exploratory	
24			
25	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
26			
27	Discussion		
28	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
29	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	
30	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
31			
32	Other information		
33	Registration	23 Registration number and name of trial registry	1-2
34	Protocol	24 Where the full trial protocol can be accessed, if available	
35	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	11
36			

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.



The effect of MELatonin on Depression, anxiety, cognitive function and sleep disturbances in patients with breast cancer. The MELODY trial: protocol for a randomized, placebo-controlled, double-blinded trial.

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000647.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Dec-2011
Complete List of Authors:	Hansen, Melissa; Herlev Hospital, University of Copenhagen, Department of Gastroenterology, Surgical Section Madsen, Michael; Herlev Hospital, University of Copenhagen, Department of Gastroenterology, Surgical Section Hageman, Ida; Rigshospitalet, University of Copenhagen, Psychiatric Center Copenhagen Rasmussen, Lars; Rigshospitalet, University of Copenhagen, Department of Anaesthesia, Centre of Head and Orthopaedics Bokmand, Susanne; Herlev Hospital, University of Copenhagen, Department of Breast Surgery Rosenberg, Jacob; Herlev Hospital, University of Copenhagen, Department of Gastroenterology, Surgical Section Gögenur, Ismail; Herlev Hospital, University of Copenhagen, Department of Gastroenterology, Surgical Section
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology, Pharmacology & therapeutics, Mental health
Keywords:	Breast surgery < SURGERY, Depression & mood disorders < PSYCHIATRY, Delirium & cognitive disorders < PSYCHIATRY, SLEEP MEDICINE, Anxiety disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS

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Manuscripts

Title page – study protocol

The effect of MELatOnin on Depression, anxiety, cognitive function and sleep disturbances in patients with breast cancer. The MELODY trial: protocol for a randomized, placebo-controlled, double-blinded trial.

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Key words: breast cancer, melatonin, depression, sleep disturbances, cognitive function

Word count: 4012

ABSTRACT

Introduction: Breast cancer represents about one third of all cancer diagnoses and accounts for about 15 % of cancer deaths in women. Many of these patients experience depression, anxiety, sleep disturbances and cognitive dysfunction. This may adversely affect quality of life but also contribute to morbidity and mortality. Melatonin is a regulatory circadian hormone having, among others, a hypnotic and an anti-depressive effect. It has very low toxicity and very few adverse effects compared with the more commonly used antidepressants and hypnotics.

Methods and analysis: The objective of this double-blind randomized, placebo-controlled trial is to investigate whether treatment with oral melatonin has a prophylactic or ameliorating effect on depressive symptoms, anxiety, sleep disturbances and cognitive dysfunction in women with breast cancer. Furthermore we will examine whether a specific clock-gene PER3 is correlated with an increased risk of depressive symptoms, sleep disturbances or cognitive dysfunction.

The MELODY-trial is a prospective double-blinded, randomized, placebo-controlled trial in which we intend to include 260 patients. The primary outcome is depressive symptoms measured by the Major Depression Inventory (MDI). The secondary outcomes are anxiety measured by a visual analogue scale (VAS), **total sleep time**, **sleep efficiency**, sleep latency and periods awake measured by actigraphy and changes in cognitive function measured by a neuropsychological test-battery. Tertiary outcomes are fatigue, pain, well-being and sleep quality/quantity measured by VAS, sleep diary and sleepiness measured by the Karolinska Sleepiness Scale. The PER3 genotype is also to be determined in blood samples.

Ethics: The study is approved by the local ethics committee (H-4-2011-007). The study has also been approved by The Danish Medicines Agency (EudraCT nr. 2010-022460-12) and The Danish Data Protection Agency (2007-58-0015/HEH.750.89-12). The project is registered on www.clinicaltrials.gov - clinicaltrials.gov identifier: NCT01355523.

INTRODUCTION

Breast cancer is the most common type of cancer among women worldwide with about 1.4 million new cases every year¹. Breast cancer accounts for 31 % of the various cancer diagnoses in women and is responsible for 15 % of deaths in females due to cancer². For Danish women it is the most common type of cancer and the incidence is rising³. The incidence rises towards the age of 65 and then the curve flattens out³. Improvement of treatment has led to increasing 5 year-survival which is now 84 % in Denmark⁴ and 89 % in the US⁵. Now focus has turned to optimizing quality of life because these patients may have a number of different psychological and physical symptoms such as depression, anxiety, fatigue, cognitive dysfunction and sleep disturbances⁶⁻¹².

METHODS

Study design and objectives

MELODY (The effect of MELatOnin on DepressioN, anxietY, cognitive function and sleep disturbances in breast cancer patients) is a prospective double-blinded, randomized, placebo-controlled trial in which we intend to include 260 patients undergoing surgery for breast cancer at Herlev University Hospital in Copenhagen, Denmark. If target sample size is not being adequately achieved, other centres/hospitals in Denmark will be invited to participate.

The objective is to investigate whether treatment with oral melatonin has a prophylactic or ameliorating effect on depressive symptoms, anxiety, sleep disturbances and cognitive dysfunction in women with breast cancer. Furthermore, we will examine whether a specific clock-gene PER3 is correlated with an increased risk of depressive symptoms, sleep disturbances or cognitive function. Patients in the intervention group will receive 6 mg oral melatonin daily 1 hour before bedtime for 1 week preoperatively to 12 weeks postoperatively. Patients in the control group will receive placebo. The melatonin/placebo will be supplied from Pharma Nord ApS, Vejle, Denmark and the tablets (melatonin/placebo) are physically identical.

Study population

Table 1: Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
<ul style="list-style-type: none"> • Female between 30-75 years • Lumpectomy or mastectomy • American Society of Anesthesiologists (ASA) class I-III • No sign of depression on Major Depression Inventory (MDI) • Not pregnant 	<ul style="list-style-type: none"> • Neoadjuvant chemotherapy • Treatment with: <ul style="list-style-type: none"> - Selective serotonin reuptake inhibitors (SSRI) - Antithrombotic drug therapy (except 75 mg acetylsalicylic acid (ASA) daily) - Monoaminoxidase (MAO) inhibitors - Calcium channel blockers • Rotor or Dubin-Johnson syndrome • Epilepsy • Known allergic reaction to melatonin • Known and treated sleep apnea • Diabetes mellitus treated with insulin • Ongoing or previous medically treated depression or bipolar disorder • Known autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis or multiple sclerosis) • Incompensated liver cirrhosis • Severe kidney disease (receiving dialysis) • Previous or other current cancer • Known medically treated sleep disorder (insomnia, restless legs etc.) • Shift-work or night-work • Daily intake of more than 5 units (1 unit = 8 g pure alcohol) • Pre-operative, continuous treatment with psychopharmacological drugs of any kind, opioids, anxiolytics or hypnotics • Predicted poor compliance • Breast-feeding • Pre-operative Mini Mental State Evaluation (MMSE) score less than 24

Approximately 1 week preoperatively patients are individually assessed and screened for inclusion. This includes a MMSE, a neuropsychological test with the ISPOCD test battery¹³ and the MDI¹⁴⁻¹⁶. Hereafter, patients will on a daily basis fill out visual analogue scales (VAS) regarding anxiety, fatigue, pain, general well-being and sleep, complete a sleep diary and fill out the Karolinska Sleepiness Scale (KSS). An Actigraph will be mounted on the wrist and worn continuously until two weeks postoperatively. Patients will be randomized to either 6 mg (2x3mg) melatonin or placebo. Patients will be instructed to take their medicine every evening at 9-10 p.m. and continue with this for 13 weeks. A blood sample will be collected for the analysis of PER3 genotype. A visit is scheduled 2 weeks postoperatively where patients are tested with the ISPOCD test battery and the MDI. At this time the Actigraph will be taken off. During the last 10 weeks of the study patients will be assessed with the MDI twice, and every two weeks fill out visual analogue scales (VAS) regarding anxiety, fatigue, pain, general well-being and sleep, complete a sleep diary and fill out the Karolinska Sleepiness Scale (KSS).

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4 At the final visit 12 weeks postoperatively patients will be tested with the ISPOCD test battery and
5 the MDI.
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7 To ensure compliance and promote participant retention and follow-up patients will throughout the
8 whole study period of 13 weeks be contacted by telephone 7 times to remind them to fill out VAS,
9 sleep diary, KSS and MDI at appropriate times, to remind them to take their tablets daily, to ask
10 about adverse reactions and to ask about diagnosis of depression since the last contact.
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14 **Criteria for discontinuing in the trial**

15 During the trial patients who experience serious peri- or postoperative complications/events,
16 causing unexpected morbidity or pain during the first postoperative days (i.e. cardiopulmonary
17 complications (myocardial infarction, serious arrhythmia, pulmonary oedema), thromboembolic
18 complications (deep venous thrombosis, pulmonary embolism), wound infection (with fever and
19 elevated WBC's and CRP) will be excluded. No further data will be collected on these patients after
20 they are excluded, previously collected data will not be analysed and the patients will not continue
21 the trial medication.
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28 The goal with medicine compliance is a minimum of 75 % compliance in the first 3 weeks and 50
29 % for the rest of the study period. Patients will be excluded if they at the visit 2 weeks
30 postoperatively have not taken at least 75 % of the study medication. No further data will be
31 collected and the patients will not continue the trial medication. Patients who have not taken at least
32 50 % of the trial medication at the last visit will not be analysed on the long-term effect variables.
33 Patients will be instructed to bring all the study medication (open and closed blister packets) with
34 them at every visit to control compliance.
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40 All potential, included and randomised patients will be accounted for in a screenings log, in an
41 identification list, in the CONSORT trial profile and in a baseline data table.
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44 **Randomization**

45 Patients who have provided written and informed consent preceding inclusion and who meet all the
46 inclusion criteria and none of the exclusion criteria are randomized to either melatonin 6 mg or
47 placebo. Inclusion and randomization is done 1 week preoperatively.
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50 The randomization is based on blocks of 6. The randomization list is computer generated using
51 dedicated software (www.randomization.com). To ensure that the randomization list is not known
52 to the investigator this procedure is completed by the pharmacy who receives the medicine directly
53 from Pharma Nord ApS, Vejle, Denmark. In case of drop-outs leading to less than 120 patients in
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4 each group, the study will include new blocks of 6 patients to ensure randomization and balance
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6 between the two groups.
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8 **Data and adverse events**

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10 Data is collected on individual paper case report forms (CRF) and data will be stored for 15 years
11 and then destroyed. Data from these CRF's will be transferred as double data entry to a database. In
12 this database patients are coded with a patient number and the database is saved on the hospitals
13 computer server to ensure maximum security. Spot checks to validate data transfer from the CRF's
14 to the electronic database will be completed by The Good Clinical Practice Unit.
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17 Due to melatonin's relative non-toxicity shown in both animal and human studies and due to the fact
18 that prolonged treatment with melatonin or melatonin receptor agonists have not shown any serious
19 adverse effects, no Data Monitoring Committee is initiated and no interim analyses have been
20 planned in the course of the study.
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23 Throughout the trial both the sponsor/investigator, who informs the patient and the patient herself,
24 will be blinded. A code breach will occur if an unexpected event arises in relation to the surgical
25 procedure and/or the postoperative period where there is a reasonable probability of an adverse
26 reaction. Unexpected events do not include procedure-related surgical/medical/anaesthetic
27 complications. Code breach is possible without prior contact to sponsor/investigator. The risk of
28 early trial termination is not existent.
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31 The summary of product characteristics (SPC) for melatonin will be used as a reference document.
32 The following known, usual side effects (1-10%) and non usual side effects (0.1-1%) will not be
33 registered as adverse events: light headache, light nausea, dyspepsia, minor symptoms of sleepiness
34 and light morning-drowsiness. Furthermore complications in relation to surgery will neither be
35 registered as adverse events.
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38 All adverse events will be registered and reported to The Danish Medicines Agency and the local
39 ethics committee in the final report. All serious adverse events will be reported to the local ethics
40 committee in an annual report together with a report on patient safety. All serious adverse reactions
41 will be reported to The Danish Medicines Agency in an annual report together with a report on
42 patient safety. The SPC for melatonin will be used to judge whether a serious adverse reaction is
43 expected/unexpected and thereby a possible sudden unexpected serious adverse reaction. The
44 sponsor/investigator will make sure that all information about sudden unexpected serious adverse
45 reaction, that are lethal or life-threatening will be registered and reported to The Danish Medicines
46 Agency as soon as possible and at the latest 7 days after sponsor/investigator has received
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4 knowledge of such a reaction. At the latest 8 days after this reporting, sponsor/investigator will
5 inform The Danish Medicines Agency of the follow-up. All other sudden unexpected serious
6 adverse reactions will be reported to The Danish Medicines Agency at the latest 15 days after
7 sponsor/investigator has gained knowledge of these. In these situations the patient will be followed
8 until the reaction has terminated – either via contact with the sponsor/investigator or via the
9 outpatient clinic at the hospital.
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14 Melatonin

15 Melatonin is a hormone which is produced at night in the corpus pineale in a rhythmical pattern,
16 controlled by an endogenous clock in the suprachiasmatic nucleus of the hypothalamus¹⁷. Its main
17 function is to synchronize the circadian rhythm¹⁷. Melatonin is mostly known for its role as a
18 circadian hormone but it also has known sedative^{18;19}, anxiolytic^{18;19}, analgesic^{20;21},
19 antihypertensive^{22;23}, non-inflammatory²⁴ and oncostatic effects²⁵⁻²⁷. Melatonin has a possible
20 antidepressive effect²⁸⁻³⁴ probably based on its effect on the central circadian regulation³⁵ and an
21 effect on improving cognitive function³⁶. Figure 1 shows the complexity of the relationship
22 between breast cancer and depression and the possible attack points of melatonin.
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30 The secretion rhythm, fluctuations and levels of melatonin have been previously investigated with
31 regards to surgery, depression and also breast cancer. After surgery melatonin secretion has shown
32 to be acutely disturbed³⁷ with a delay of secretion and reduced amplitude^{38;39}. Various lines of
33 evidence show that depressed patients exhibit disturbances in both the amplitude and the shape of
34 the melatonin secretion rhythm, with some studies showing a low nocturnal melatonin secretion and
35 others showing an increase in secretion³⁵. A growing amount of evidence from prospective studies
36 suggest an association between night work and breast cancer risk, most likely due to subsequent
37 melatonin suppression⁴⁰.
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43 Melatonin is relatively non-toxic⁴¹⁻⁴³. Animal studies have shown that the maximum dose given in
44 vivo, without any adverse effects or death is 200 mg/kg for pregnant rats throughout the whole
45 pregnancy and 800 mg/kg for mice^{44;45}. The drug has been used in many clinical studies of both
46 adults^{18-20;22;41;42;46;47} and newborns^{48;49} without serious adverse effects. Doses of 1000 mg daily for
47 one month have been given and the only reported adverse effect was drowsiness⁴¹. In a recent
48 systematic review the most often reported side effects were headache, dizziness, nausea and
49 drowsiness⁵⁰.
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PER3 clock-gene

Previous studies have shown that certain genes, called clock-genes, have a role in regulating circadian rhythms and sleep in humans⁵¹. A coding region in the clock-gene PER3, which is repeated in either 4 or 5 units has been coupled to various phenotypical traits; A or B people, sleep diseases⁵²⁻⁵⁴, affective disorders^{55;56}, cognitive function after sleep deprivation^{54;57} and in one study⁵⁸ a relationship was found between the 5/5 or 4/5 genotype of the PER3 gene and breast cancer. We would like to investigate whether sleep quality, cognitive function or depressive symptoms are correlated with any of these three PER3 genotypes.

Ethics

The study will be performed in agreement with the Helsinki II declaration and law 503 of 1992 about the Scientific Ethics Committee System and is approved by the local ethics committee (H-4-2011-007). The study has also been approved by The Danish Medicines Agency (EudraCT nr. 2010-022460-12) and The Danish Data Protection Agency (2007-58-0015/HEH.750.89-12). The project is registered on www.clinicaltrials.gov as recommended by the International Committee of Medical Journal Editors - clinicaltrials.gov identifier: NCT01355523. **The Good Clinical Practice Unit at Copenhagen University will oversee the trial and conduct trial audit periodically. All authors will have direct access to data during and after the trial. Furthermore the sponsor investigator will allow direct access to source data/documents, including patient charts, at monitoring, audit and/or inspection from The Danish Medicines Agency, The Good Clinical Practice Unit or from health authorities from other countries.**

EFFECT PARAMETERS

Table 2: Effect parameters

PRIMARY EFFECT PARAMETER	SECONDARY EFFECT PARAMETERS	TERTIARY EFFECT PARAMETERS
<ul style="list-style-type: none"> MDI (Major Depression Inventory) 	<ul style="list-style-type: none"> Anxiety measured by VAS Total sleep time, sleep efficiency, sleep latency and periods awake measured by actigraphy Changes in cognitive function measured by a neuropsychological test-battery PER3 genotype correlated with sleep, cognitive function and depressive symptoms 	<ul style="list-style-type: none"> Fatigue, pain, well-being and sleep quality/quantity measured by VAS Sleep diary Sleepiness measured by the Karolinska Sleepiness Scale

Major Depression Inventory (MDI)

Major Depression Inventory is a self-rating scale including 12 questions. The questionnaire is already well documented in a Danish population¹⁴. The questions cover the 10 ICD-10 questions for depression and the symptoms are identical with the DSM-IV major depression diagnosis apart from one symptom, low self esteem (question 4), which in DSM-IV is incorporated in the question about guilt (question 5). The MDI includes 10 items, where item 8 and 10 are divided into two sub-questions a and b. For item 8 and 10 the highest score of question a and b is included. The individual items are measured on a 6-point Likert scale with graduations depending on the extent of the symptom the last 14 days; 0 (the symptom has not been present) till 5 (the symptom has been present continuously).

The MDI has a dual function. It can be used as a diagnostic tool where it can, by algorithms, lead to either DSM-IV or ICD-10 categories of “major” or “moderate to severe depression”. An acceptable sensitivity and specificity for the diagnosis of depression according to ICD-10 and DSM-III/DSM-IV has previously been found¹⁵. The MDI can also be used as a measuring instrument to indicate the severity of the depression. Thus, the MDI correlates with the Hamiltons Depressions Scale (HAM-D)¹⁶.

Actigraphy

Actigraphy is a well known non-invasive method to objectively measure sleep. Using an Actigraph, activity levels are registered by a wrist-worn mini-computer. This method which does not disturb the patients' sleep has been used for many years⁵⁹ and also in the postoperative setting⁶⁰. It has been shown that actigraphy has a high sensitivity and specificity for detecting sleep start, sleep periods and awakenings⁵⁹. **The gold standard for measuring sleep is polysomnography. Actigraphy has a high specificity for detecting whether the patient is asleep or awake but can not differentiate between sleep stages and score REM sleep.**

An actigraph measures small accelerations with a piezo-electrode and stores this in a memory. Data can be recorded via different modalities and we will be using the zero crossing method, where all accelerations (> 0.1G) which cross a certain threshold (0 or very close to 0) will be detected. The sleep analysis will be performed by dedicated software (Action4 software, Ambulatory Monitoring Inc., NY, USA) by using the Cole-Kripke algorithm⁶¹. Data will be reported as total sleep time per period, sleep efficiency, sleep ratio, number of awakenings and duration of awakenings. The method is validated and has been used previously to measure sleep in patients with breast cancer before, during and after surgery⁶²⁻⁶⁵.

The ISPOCD neuropsychological test battery

The cognitive function of the patients will be tested preoperatively and at 2 weeks and 3 months postoperatively. The test battery consists of 4 validated tests: the Visual Verbal Learning Test, the Stroop Colour-Word Test, the Letter-Digit Coding Test and the Concept Shifting Task.

The test battery takes approximately 45 minutes to complete and has been used previously in the large multicenter ISPOCD trial¹³.

Anxiety and sleep quality measurements

A subjective feeling of anxiety will be registered on a VAS going from “no anxiety” to “worst possible anxiety”. Measurements will take place daily for the first three weeks of the study and every two weeks for the last 10 weeks.

Subjective sleep quality will be registered on a VAS going from “best possible sleep” equivalent to 0 mm to “worst possible sleep” equivalent to 100 mm. Patients will also fill out VAS regarding general well-being, fatigue and pain. Measurements will take place at the same time as for anxiety. Furthermore, a sleep diary recording sleep time and awakening time, will be completed daily for the first 3 weeks of the study and thereafter every 14 days. Patients will at the same time periods complete the KSS which is used to quantify levels of sleepiness. KSS is a 9 point scale from 1 (very awake) to 9 (very sleepy), where a score of 7 or more reflects pathological sleepiness⁶⁶.

Other collected data

Age, weight, height, menopausal status, educational level, cohabitation status, work market affiliation, household income, number of children/number of children living at home, smoking habits, ASA class, duration of surgery, the size of the incision, consumption of analgesics postoperatively and which postoperative oncological treatment each patient receives after surgery.

STATISTICAL ANALYSIS AND SAMPLE SIZE CALCULATION

The sample size estimation is based on a conservative estimate of the incidence of depression of 30% in breast cancer patients⁷ with a reduction to 15% with melatonin treatment. With a power of 80%, a risk of type I error of 5% and a risk of type II error of 20% we should include 120 patients in each group receiving melatonin or placebo. We have chosen to include 130 patients in each group.

Statistical analyses will be done using SPSS Version 18.0.

Regarding our primary outcome mean MDI total scores and prevalences of ICD-10 mild, moderate and severe depression will be calculated for both samples. Normality of the data will be tested by

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4 one sample Kolmogorov-Smirnov test and parametric or non-parametric statistics will be used
5 accordingly. The two groups will be compared by Fisher's exact test for the primary outcome.
6 Paired Student's t-test or Wilcoxon test will be used for intra-group comparisons and unpaired
7 Student's t-test or Mann-Whitney's test for inter-group comparisons. For repeated measures
8 Friedman test or an ANOVA will be used when appropriate.

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10 For comparing anxiety by VAS and sleep architecture (objective data from the Actigraph) we will
11 do inter-group comparisons with Mann-Whitney's test and intra-group comparisons using the
12 Wilcoxon signed rank test.

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14 For analyzing POCD in the two groups we will use 2x2 tables and a Fisher's exact test. Patients will
15 be defined as having POCD if 2 of the seven Z-scores in individual test or the combined Z-score are
16 1.96 or more¹³. ANOVA will be used to analyze the 2 groups and the specific Z-scores for the
17 seven subtests and the combined Z-scores. A Bonferroni correction will be made when performing
18 multiple comparisons.

19
20 For analyses of correlation between PER3 genotype and sleep, cognitive function and depressive
21 symptoms a logistic regression analysis will be used. For the subjective parameters fatigue, pain,
22 general wellbeing and sleep quality/quantity measured by VAS and sleepiness by KSS we will do
23 inter-group comparisons with the Mann Whitney test and intra-group comparisons using the
24 Wilcoxon signed rank test. We plan to do intention-to-treat as well as per protocol analyses. In
25 general, $p < 0.05$ will be considered statistically significant.

26 27 28 29 30 31 32 33 34 35 36 37 **DISCUSSION**

38
39 There is a complex relationship between depression and breast cancer with influence from various
40 factors – figure 1. Due to the high frequencies of depression, anxiety, sleep disturbances and
41 cognitive dysfunction in patients with breast cancer, a high interest is found in preventing these co-
42 morbid symptoms.

43
44 Depression is both underdiagnosed and undertreated in many cancer patients^{11;67}, especially those
45 with breast cancer⁶⁸. The overall rate of depression in patients with breast cancer is higher than in
46 most cancers. This is most likely because menopause, either naturally occurring or premature due to
47 the effects of chemotherapy and/or anti-hormone treatment, and estrogen decline are related to
48 depression⁶. It has been shown that up to 50 % of patients with breast cancer may experience
49 depression and/or anxiety within the first year of diagnosis⁷. Concomitant breast cancer and
50 depression is associated with higher mortality and morbidity^{67;69-72} but also lower patient
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4 satisfaction⁷³ and compliance to adjuvant therapy⁷⁴ and general medical treatment⁷⁵. Even a year
5 after surgery many women still deal with an anxiety problem⁷⁶ and about 15 % are still depressed⁷.
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7 Studies have shown that treating anxiety and depression in these patients with breast cancer
8
9 improves their quality of life, leads to a higher completion of adjuvant therapy and extends their
10
11 lifetime^{68;77;78}. Therefore it is important to optimize the treatment of these symptoms.

12
13 A number of randomized controlled trials have examined the efficacy of antidepressants compared
14 with placebo in patients with breast cancer⁷⁸⁻⁸⁵. A high number of drop-outs due to side effects
15 related to the antidepressant treatment have also rendered such trials difficult to complete^{79;84;86}.
16
17 Furthermore, recent evidence indicates that some selective serotonin reuptake inhibitor
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19 antidepressants may reduce tamoxifen's effectiveness and are associated with an increased risk of
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21 mortality^{87;88}.

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23 Sleep disturbances are a frequent problem in cancer patients^{89;90}. Compared with other types of
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25 cancer breast cancer is associated with an exceptionally high rate of reduced sleep quality^{10;89}
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27 which can be found even many years after end of treatment⁸. The estimated prevalence of sleep
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29 problems among patients with breast cancer is between 38-61%^{10;89;91;92}, and it may reduce quality
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31 of life in this group of patients^{91;93}. About 30 % of patients with breast cancer take hypnotics^{10;89;92}
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33 leading to a potential dependency problem and it is therefore important to focus on treatments with
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35 less adverse effects.

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37 The sleep disturbances can be due to a variety of factors, both physical and psychological, which all
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39 have a mutual influence on each other. Among the psychological factors, depression and anxiety are
40
41 well-known and these patients also exhibit a change in sleep architecture⁹⁴. In general, depressed
42
43 patients display sleep abnormalities such as difficulties falling asleep and staying asleep, loss of
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45 slow-wave-sleep and changed REM sleep⁹⁵. Pain and hot flushes are examples of the physical
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47 factors^{8;91;92}.

48
49 Overall, it is difficult to conclude whether sleep disturbances are a precursor or a sequelae of
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51 depression. Various studies in healthy individuals have shown a causal relationship between sleep
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53 disturbances and the following development of depression^{96;97}. More specifically for patients with
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55 breast cancer, a circadian rhythm disruption has been associated with depression, fatigue and pain
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57 ^{62;63;65;98}. Altogether there is a complicated relationship between circadian disturbances, sleep and
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59 mood³⁵ and this is especially prevalent in patients with breast cancer⁹⁹.

60
Disturbances of cognitive function are a prevalent phenomenon in patients with breast cancer and
can influence the general quality of life in this group of patients^{9;12}. Studies have suggested that the

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4 cancer *per se* and/or the treatment with surgery, radiation, chemotherapy and hormone therapy or
5 genetics can be contributing factors in the development of cognitive disturbances^{100;101}. POCD
6 (postoperative cognitive dysfunction) is characterized by a deterioration in memory, concentration
7 and information assessment after surgery¹³.
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9
10 In other settings some studies have shown that melatonin can attenuate cognitive dysfunction
11^{36;102;103} and this mechanism together with the general improvement of sleep could be beneficial on
12 cognitive disturbances in this specific group of patients. Since there is no specific knowledge on this
13 topic with regards to breast cancer it is necessary to investigate whether the development of
14 cognitive problems can be prevented by melatonin treatment.
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20 In conclusion we hope, with this project, to decrease the occurrence of depression, anxiety, sleep
21 disturbances and cognitive dysfunction in patients with breast cancer and in a larger perspective
22 reduce morbidity and mortality and improve quality of life for these patients. With regards to
23 genetics this project could lead to the possibility of being able to detect women with a higher risk of
24 developing the abovementioned problems and then give indication for selective prophylactic
25 treatment. The diversity of melatonin's physiological functions and treatment effects are
26 continuously being investigated in both animal and human studies. To-date, the effect of melatonin
27 in a breast cancer population with the above-mentioned indications has not yet been studied.
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35 Conflict of interest statement:

36 No conflicts of interest.
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40 Funding statement:

41 This work was supported by grants from the University of Copenhagen, The Aase and Ejnar
42 Danielsens Foundation, The A.P.Møller Foundation for the Advancement of Medical Science, The
43 Else and Mogens Wedell Wedellborgs Foundation, The Beckett Foundation, The Hede Nielsen
44 Family Foundation, The Dagmar Marshalls Foundation and Manufacturer Einar Willumsen's
45 Memorial Scholarship. **These abovementioned funders have had no influence on the study design,**
46 **will have no influence on collection, management, analysis and interpretation of data, writing of the**
47 **report or the decision to submit the report for publication. All these activities are done by the**
48 **authors.** Pharma Nord provided the melatonin and placebo tablets but had no influence on the study
49 design and will have no influence on the interpretation of results.
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Contributorship Statement

All authors have participated in making substantial contributions to conception and design, drafting the article or revising it critically for important intellectual content and all authors have approved the final version to be published.

Reference List

- (1) <http://globocan.iarc.fr/factsheets/cancers/breast.asp> (accessed November 2011).
- (2) Greenlee RT, Hill-Harmon MB, Murray T et al. . Cancer statistics, 2001. *CA Cancer J Clin* 2001;**51**:15-36.
- (3) http://www.sst.dk/publ/Publ2009/DOKU/cancerreg/cancerregisteret_2008.pdf (accessed November 2011).
- (4) <http://www.sst.dk/publ/Publ2010/DOKU/SygehusbaseretOverlevelse/SygehuspatientersOverlevelse1997-2008.pdf> (accessed November 2011).
- (5) <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-030975.pdf> (accessed November 2011).
- (6) Fann JR, Thomas-Rich AM, Katon WJ et al. Major depression after breast cancer: a review of epidemiology and treatment. *Gen Hosp Psychiatry* 2008;**30**:112-126.

- 1
2
3
4 (7) Burgess C, Cornelius V, Love S et al. Depression and anxiety in women with early breast
5 cancer: five year observational cohort study. *BMJ* 2005;**330**:702-705.
6
7
8
9
10 (8) Otte JL, Carpenter JS, Russell KM et al. Prevalence, Severity, and Correlates of Sleep-Wake
11 Disturbances in Long-Term Breast Cancer Survivors. *J Pain Symptom Manage*
12 2010;**39**:535-547.
13
14
15
16
17 (9) Debess J, Riis JO, Pedersen L et al. Cognitive function and quality of life after surgery for
18 early breast cancer in North Jutland, Denmark. *Acta Oncol* 2009;**48**:532-540.
19
20
21
22 (10) Savard J, Simard S, Blanchet J et al. Prevalence, clinical characteristics, and risk factors for
23 insomnia in the context of breast cancer. *Sleep* 2001;**24**:583-590.
24
25
26
27
28 (11) Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr*
29 2004;**32**:57-71.
30
31
32
33 (12) Schou I, Ekeberg O, Sandvik L et al. Multiple predictors of health-related quality of life in
34 early stage breast cancer. Data from a year follow-up study compared with the general
35 population. *Qual Life Res* 2005;**14**:1813-1823.
36
37
38
39
40 (13) Moller JT, Cluitmans P, Rasmussen LS et al. Long-term postoperative cognitive dysfunction
41 in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative
42 Cognitive Dysfunction. *Lancet* 1998;**351**:857-861.
43
44
45
46
47
48 (14) Olsen LR, Mortensen EL, Bech P. Prevalence of major depression and stress indicators in
49 the Danish general population. *Acta Psychiatr Scand* 2004;**109**:96-103.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (15) Bech P, Rasmussen NA, Olsen LR et al. The sensitivity and specificity of the Major
5
6 Depression Inventory, using the Present State Examination as the index of diagnostic
7
8 validity. *J Affect Disord* 2001;**66**:159-164.
9
10
11 (16) Olsen LR, Jensen DV, Noerholm V et al. The internal and external validity of the Major
12
13 Depression Inventory in measuring severity of depressive states. *Psychol Med* 2003;**33**:351-
14
15 356.
16
17
18 (17) Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin.
19
20
21 *Sleep Med Rev* 2005;**9**:11-24.
22
23
24 (18) Acil M, Basgul E, Celiker V et al. Perioperative effects of melatonin and midazolam
25
26 premedication on sedation, orientation, anxiety scores and psychomotor performance. *Eur J*
27
28 *Anaesthesiol* 2004;**21**:553-557.
29
30
31 (19) Naguib M, Samarkandi AH. Premedication with melatonin: a double-blind, placebo-
32
33 controlled comparison with midazolam. *Br J Anaesth* 1999;**82**:875-880.
34
35
36 (20) Caumo W, Torres F, Moreira NL, Jr. et al. The clinical impact of preoperative melatonin on
37
38 postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg*
39
40 2007;**105**:1263-71.
41
42
43 (21) Srinivasan V, Pandi-Perumal SR, Spence DW et al. Potential use of melatonergic drugs in
44
45 analgesia: mechanisms of action. *Brain Res Bull* 2010;**81**:362-371.
46
47
48 (22) Cagnacci A, Cannoletta M, Renzi A et al. Prolonged melatonin administration decreases
49
50 nocturnal blood pressure in women. *Am J Hypertens* 2005;**18**:1614-1618.
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (23) Kitajima T, Kanbayashi T, Saitoh Y et al. The effects of oral melatonin on the autonomic
5 function in healthy subjects. *Psychiatry Clin Neurosci* 2001;**55**:299-300.
6
7
8
9 (24) Maestroni GJ. The immunotherapeutic potential of melatonin. *Expert Opin Investig Drugs*
10 2001;**10**:467-476.
11
12
13
14 (25) Vijayalaxmi, Thomas CR, Jr., Reiter RJ et al. Melatonin: from basic research to cancer
15 treatment clinics. *J Clin Oncol* 2002;**20**:2575-2601.
16
17
18
19 (26) Reiter RJ. Mechanisms of cancer inhibition by melatonin. *J Pineal Res* 2004;**37**:213-214.
20
21
22
23 (27) Grant SG, Melan MA, Latimer JJ et al. Melatonin and breast cancer: cellular mechanisms,
24 clinical studies and future perspectives. *Expert Rev Mol Med* 2009;**11**:e5.
25
26
27
28 (28) Bellipanni G, Di MF, Blasi F, Di MA. Effects of melatonin in perimenopausal and
29 menopausal women: our personal experience. *Ann N Y Acad Sci* 2005;**1057**:393-402.
30
31
32
33 (29) Kopp C, Vogel E, Rettori MC et al. The effects of melatonin on the behavioural
34 disturbances induced by chronic mild stress in C3H/He mice. *Behav Pharmacol* 1999;**10**:73-
35 83.
36
37
38
39 (30) Hickie IB, Rogers NL. Novel melatonin-based therapies: potential advances in the treatment
40 of major depression. *Lancet* 2011;**378**:621-631.
41
42
43
44 (31) Serfaty MA, Osborne D, Buszewicz MJ et al. A randomized double-blind placebo-
45 controlled trial of treatment as usual plus exogenous slow-release melatonin (6 mg) or
46 placebo for sleep disturbance and depressed mood. *Int Clin Psychopharmacol* 2010;**25**:132-
47 142.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (32) Spadoni G, Bedini A, Rivara S et al. Melatonin Receptor Agonists: New Options for
5
6 Insomnia and Depression Treatment. *CNS Neurosci Ther* Published Online First: 15 October
7
8 2010. doi: 10.1111/j.1755-5949.2010.00197
9
- 10
11 (33) Garzon C, Guerrero JM, Aramburu O et al. Effect of melatonin administration on sleep,
12
13 behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-
14
15 blind, placebo-controlled study. *Aging Clin Exp Res* 2009;**21**:38-42.
16
17
- 18
19 (34) Rahman SA, Kayumov L, Shapiro CM. Antidepressant action of melatonin in the treatment
20
21 of Delayed Sleep Phase Syndrome. *Sleep Med* 2010;**11**:131-136.
22
23
- 24 (35) Srinivasan V, Pandi-Perumal SR, Trakht I et al. Pathophysiology of depression: role of sleep
25
26 and the melatonergic system. *Psychiatry Res* 2009;**165**:201-214.
27
28
- 29
30 (36) Furio AM, Brusco LI, Cardinali DP. Possible therapeutic value of melatonin in mild
31
32 cognitive impairment: a retrospective study. *J Pineal Res* 2007;**43**:404-409.
33
34
- 35 (37) Ram E, Vishne TH, Weinstein T et al. General anesthesia for surgery influences melatonin
36
37 and cortisol levels. *World J Surg* 2005;**29**:826-829.
38
39
- 40 (38) Karkela J, Vakkuri O, Kaukinen S et al. The influence of anaesthesia and surgery on the
41
42 circadian rhythm of melatonin. *Acta Anaesthesiol Scand* 2002;**46**:30-36.
43
44
- 45 (39) Gogenur I, Middleton B, Kristiansen VB et al. Disturbances in melatonin and core body
46
47 temperature circadian rhythms after minimal invasive surgery. *Acta Anaesthesiol Scand*
48
49 2007;**51**:1099-1106.
50
51
- 52
53 (40) Megdal SP, Kroenke CH, Laden F et al. Night work and breast cancer risk: a systematic
54
55 review and meta-analysis. *Eur J Cancer* 2005;**41**:2023-2032.
56
57
58
59
60

- 1
2
3
4 (41) Nordlund JJ, Lerner AB. The effects of oral melatonin on skin color and on the release of
5
6 pituitary hormones. *J Clin Endocrinol Metab* 1977;**45**:768-774.
7
8
- 9 (42) Nickkholgh A, Schneider H, Sobirey M et al. The use of high-dose melatonin in liver
10
11 resection is safe: first clinical experience. *J Pineal Res* 2011;**50**:381-388.
12
13
- 14 (43) Seabra ML, Bignotto M, Pinto LR, Jr. et al. Randomized, double-blind clinical trial,
15
16 controlled with placebo, of the toxicology of chronic melatonin treatment. *J Pineal Res*
17
18 2000;**29**:193-200.
19
20
- 21 (44) Jahnke G, Marr M, Myers C et al. Maternal and developmental toxicity evaluation of
22
23 melatonin administered orally to pregnant Sprague-Dawley rats. *Toxicol Sci* 1999;**50**:271-
24
25 279.
26
27
- 28 (45) Barchas J, DaCosta F, Spector S. Acute pharmacology of melatonin. *Nature* 1967;**214**:919-
29
30 920.
31
32
- 33 (46) Shaw KM, Stern GM, Sandler M. Melatonin and parkinsonism. *Lancet* 1973;**1**:271.
34
35
36
- 37 (47) Zhdanova IV, Wurtman RJ, Morabito C et al. Effects of low oral doses of melatonin, given
38
39 2-4 hours before habitual bedtime, on sleep in normal young humans. *Sleep* 1996;**19**:423-
40
41 431.
42
43
- 44 (48) Gitto E, Romeo C, Reiter RJ et al. Melatonin reduces oxidative stress in surgical neonates. *J*
45
46 *Pediatr Surg* 2004;**39**:184-189.
47
48
- 49 (49) Gitto E, Karbownik M, Reiter RJ et al. Effects of melatonin treatment in septic newborns.
50
51 *Pediatr Res* 2001;**50**:756-760.
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (50) Buscemi N, Vandermeer B, Hooton N et al. Efficacy and safety of exogenous melatonin for
5 secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis.
6
7
8 *BMJ* 2006;**332**:385-393.
9
- 10
11 (51) Dijk DJ, Archer SN. PERIOD3, circadian phenotypes, and sleep homeostasis. *Sleep Med*
12
13 *Rev* 2010;**14**:151-160.
14
- 15
16 (52) Archer SN, Robilliard DL, Skene DJ et al. A length polymorphism in the circadian clock
17 gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep*
18
19 2003;**26**:413-415.
20
21
22
23
- 24 (53) Johansson C, Willeit M, Smedh C et al. Circadian clock-related polymorphisms in seasonal
25 affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology*
26
27 2003;**28**:734-739.
28
29
30
- 31 (54) Viola AU, Archer SN, James LM et al. PER3 polymorphism predicts sleep structure and
32 waking performance. *Curr Biol* 2007;**17**:613-618.
33
34
35
36
- 37 (55) Nievergelt CM, Kripke DF, Barrett TB et al. Suggestive evidence for association of the
38 circadian genes PERIOD3 and ARNTL with bipolar disorder. *Am J Med Genet B*
39
40 *Neuropsychiatr Genet* 2006;**141B**:234-241.
41
42
43
44
- 45 (56) Artioli P, Lorenzi C, Pirovano A et al. How do genes exert their role? Period 3 gene variants
46 and possible influences on mood disorder phenotypes. *Eur Neuropsychopharmacol*
47
48 2007;**17**:587-594.
49
50
- 51 (57) Groeger JA, Viola AU, Lo JC et al. Early morning executive functioning during sleep
52 deprivation is compromised by a PERIOD3 polymorphism. *Sleep* 2008;**31**:1159-1167.
53
54
55
56
57
58
59
60

- 1
2
3
4 (58) Zhu Y, Brown HN, Zhang Y et al. Period3 structural variation: a circadian biomarker
5 associated with breast cancer in young women. *Cancer Epidemiol Biomarkers Prev*
6 2005;**14**:268-270.
7
8
9
10
11 (59) Ancoli-Israel S, Cole R, Alessi C et al. The role of actigraphy in the study of sleep and
12 circadian rhythms. *Sleep* 2003;**26**:342-392.
13
14
15
16
17 (60) Bisgaard T, Kjaersgaard M, Bernhard A et al. Computerized monitoring of physical activity
18 and sleep in postoperative abdominal surgery patients. *J Clin Monit Comput* 1999;**15**:1-8.
19
20
21
22 (61) Cole RJ, Kripke DF, Gruen W et al. Automatic sleep/wake identification from wrist activity.
23 *Sleep* 1992;**15**:461-469.
24
25
26
27
28 (62) Berger AM, Wielgus K, Hertzog M et al. Patterns of circadian activity rhythms and their
29 relationships with fatigue and anxiety/depression in women treated with breast cancer
30 adjuvant chemotherapy. *Support Care Cancer* 2010;**18**:105-114.
31
32
33
34
35 (63) Wright CE, Bovbjerg DH, Montgomery GH et al. Disrupted sleep the night before breast
36 surgery is associated with increased postoperative pain. *J Pain Symptom Manage*
37 2009;**37**:352-362.
38
39
40
41
42
43 (64) Ancoli-Israel S, Liu L, Marler MR et al. Fatigue, sleep, and circadian rhythms prior to
44 chemotherapy for breast cancer. *Support Care Cancer* 2006;**14**:201-209.
45
46
47
48
49 (65) Roscoe JA, Morrow GR, Hickok JT et al. Temporal interrelationships among fatigue,
50 circadian rhythm and depression in breast cancer patients undergoing chemotherapy
51 treatment. *Support Care Cancer* 2002;**10**:329-336.
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (66) Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J*
5 *Neurosci* 1990;**52**:29-37.
6
7
8
9 (67) Caplette-Gingras A, Savard J. Depression in women with metastatic breast cancer: a review
10 of the literature. *Palliat Support Care* 2008;**6**:377-387.
11
12
13 (68) Somerset W, Stout SC, Miller AH et al. Breast cancer and depression. *Oncology*
14 2004;**18**:1021-1034.
15
16
17 (69) Hjerl K, Andersen EW, Keiding N et al. Depression as a prognostic factor for breast cancer
18 mortality. *Psychosomatics* 2003;**44**:24-30.
19
20
21 (70) Watson M, Haviland JS, Greer S et al. Influence of psychological response on survival in
22 breast cancer: a population-based cohort study. *Lancet* 1999;**354**:1331-1336.
23
24
25 (71) Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and
26 mortality in cancer patients: a meta-analysis. *Cancer* 2009;**115**:5349-5361.
27
28
29 (72) Abrams TE, Vaughan-Sarrazin M, Rosenthal GE. Influence of psychiatric comorbidity on
30 surgical mortality. *Arch Surg* 2010;**145**:947-953.
31
32
33 (73) Bui QU, Ostir GV, Kuo YF et al. Relationship of depression to patient satisfaction: findings
34 from the barriers to breast cancer study. *Breast Cancer Res Treat* 2005;**89**:23-28.
35
36
37 (74) Colleoni M, Mandala M, Peruzzotti G et al. Depression and degree of acceptance of
38 adjuvant cytotoxic drugs. *Lancet* 2000;**356**:1326-1327.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (75) DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with
5
6 medical treatment: meta-analysis of the effects of anxiety and depression on patient
7
8 adherence. *Arch Intern Med* 2000;**160**:2101-2107.
9
10
11 (76) Hartl K, Schennach R, Muller M et al. Quality of life, anxiety, and oncological factors: a
12
13 follow-up study of breast cancer patients. *Psychosomatics* 2010;**51**:112-123.
14
15
16 (77) Giese-Davis J, Collie K, Rancourt KM et al. Decrease in depression symptoms is associated
17
18 with longer survival in patients with metastatic breast cancer: a secondary analysis. *J Clin*
19
20 *Oncol* 2011;**29**:413-420.
21
22
23 (78) Navari RM, Brenner MC, Wilson MN. Treatment of depressive symptoms in patients with
24
25 early stage breast cancer undergoing adjuvant therapy. *Breast Cancer Res Treat*
26
27 2008;**112**:197-201.
28
29
30 (79) Pezzella G, Moslinger-Gehmayr R, Contu A. Treatment of depression in patients with breast
31
32 cancer: a comparison between paroxetine and amitriptyline. *Breast Cancer Res Treat*
33
34 2001;**70**:1-10.
35
36
37 (80) Roscoe JA, Morrow GR, Hickok JT et al. Effect of paroxetine hydrochloride (Paxil) on
38
39 fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res*
40
41 *Treat* 2005;**89**:243-249.
42
43
44 (81) van HK, Zivkov M. Pharmacological treatment of depression in cancer patients. A placebo-
45
46 controlled study of mianserin. *Br J Psychiatry* 1996;**169**:440-443.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

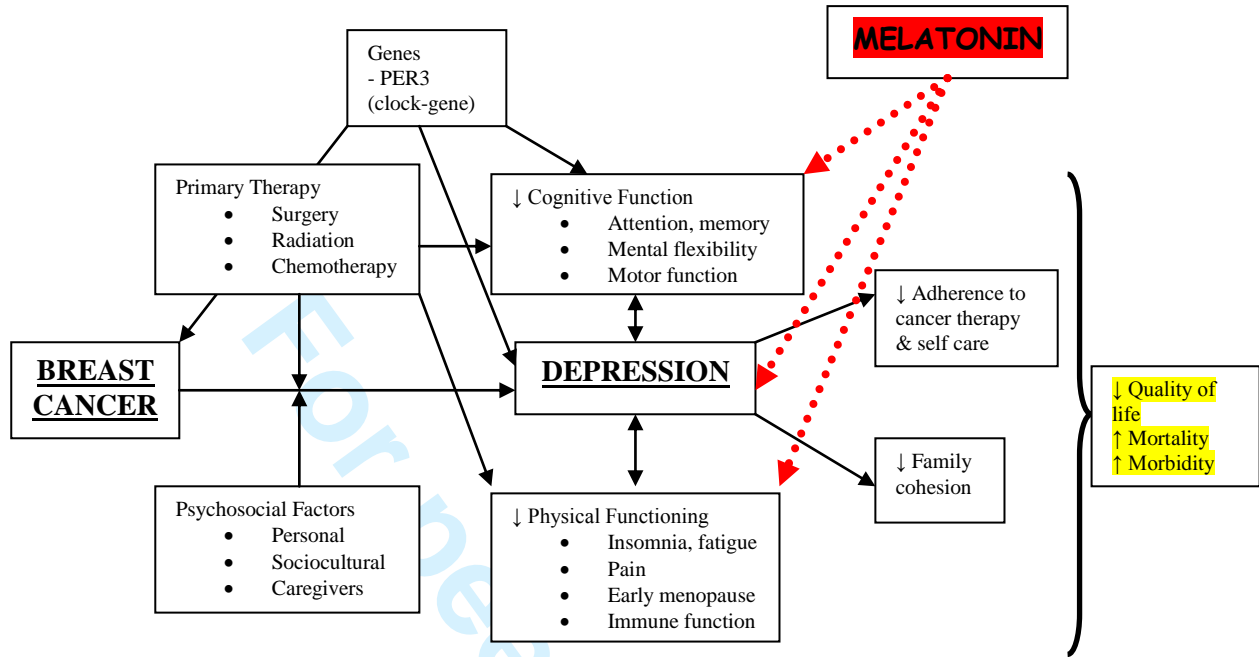
- 1
2
3
4 (82) Musselman DL, Somerset WI, Guo Y et al. A double-blind, multicenter, parallel-group
5 study of paroxetine, desipramine, or placebo in breast cancer patients (stages I, II, III, and
6 IV) with major depression. *J Clin Psychiatry* 2006;**67**:288-296.
7
8
9
10
11 (83) Grassi L, Biancosino B, Marmai L et al. Effect of reboxetine on major depressive disorder in
12 breast cancer patients: an open-label study. *J Clin Psychiatry* 2004;**65**:515-520.
13
14
15
16
17 (84) Fisch MJ, Loehrer PJ, Kristeller J et al. Fluoxetine versus placebo in advanced cancer
18 outpatients: a double-blinded trial of the Hoosier Oncology Group. *J Clin Oncol*
19 2003;**21**:1937-1943.
20
21
22
23
24 (85) Morrow GR, Hickok JT, Roscoe JA et al. Differential effects of paroxetine on fatigue and
25 depression: a randomized, double-blind trial from the University of Rochester Cancer Center
26 Community Clinical Oncology Program. *J Clin Oncol* 2003;**21**:4635-4641.
27
28
29
30
31
32 (86) Pirl WF, Roth AJ. Diagnosis and treatment of depression in cancer patients. *Oncology*
33 1999;**13**:1293-1301.
34
35
36
37
38 (87) Kelly CM, Juurlink DN, Gomes T et al. Selective serotonin reuptake inhibitors and breast
39 cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ*
40 2010;**340**:c693.
41
42
43
44
45 (88) Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via
46 cytochrome P450 2D6. *J Clin Psychiatry* 2009;**70**:1688-1697.
47
48
49
50
51 (89) Davidson JR, MacLean AW, Brundage MD et al. Sleep disturbance in cancer patients. *Soc*
52 *Sci Med* 2002;**54**:1309-1321.
53
54
55
56
57
58
59
60

- 1
2
3
4 (90) Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J*
5
6 *Clin Oncol* 2001;**19**:895-908.
7
8
9 (91) Fortner BV, Stepanski EJ, Wang SC et al. Sleep and quality of life in breast cancer patients.
10
11 *J Pain Symptom Manage* 2002;**24**:471-480.
12
13 (92) Koopman C, Nouriani B, Erickson V et al. Sleep disturbances in women with metastatic
14
15 breast cancer. *Breast J* 2002;**8**:362-370.
16
17 (93) Dow KH, Ferrell BR, Leigh S et al. An evaluation of the quality of life among long-term
18
19 survivors of breast cancer. *Breast Cancer Res Treat* 1996;**39**:261-273.
20
21 (94) Morin CM, Ware JC. Sleep and psychopathology. *Appl Prev Psychol* 1996;**5**:211-224.
22
23 (95) Benca RM, Okawa M, Uchiyama M et al. Sleep and mood disorders. *Sleep Med Rev*
24
25 1997;**1**:45-56.
26
27 (96) Breslau N, Roth T, Rosenthal L et al. Sleep disturbance and psychiatric disorders: a
28
29 longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;**39**:411-418.
30
31 (97) Livingston G, Blizard B, Mann A. Does sleep disturbance predict depression in elderly
32
33 people? A study in inner London. *Br J Gen Pract* 1993;**43**:445-448.
34
35 (98) Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer
36
37 patients: a review. *Eur J Cancer Care (Engl)* 2001;**10**:245-255.
38
39 (99) Palesh OG, Collie K, Batiuchok D et al. A longitudinal study of depression, pain, and stress
40
41 as predictors of sleep disturbance among women with metastatic breast cancer. *Biol Psychol*
42
43 2007;**75**:37-44.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 (100) Wefel JS, Lenzi R, Theriault R et al. 'Chemobrain' in breast carcinoma?: a prologue. *Cancer*
5
6 2004;**101**:466-475.
7
8
9 (101) Jim HS, Donovan KA, Small BJ et al. Cognitive functioning in breast cancer survivors: a
10
11 controlled comparison. *Cancer* 2009;**115**:1776-1783.
12
13
14 (102) Manda K, Reiter RJ. Melatonin maintains adult hippocampal neurogenesis and cognitive
15
16 functions after irradiation. *Prog Neurobiol* 2010;**90**:60-68.
17
18
19 (103) Sharma AK, Mehta AK, Rathor N et al. Melatonin attenuates cognitive dysfunction and
20
21 reduces neural oxidative stress induced by phosphamidon. *Fundam Clin Pharmacol*
22
23
24 Published Online First: 26 July 2011. doi: 10.1111/j.1472-8206.2011.00977.x
25
26
27
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Figure 1: The relationship between breast cancer and depression



Modified after Fann JR et al. 2008 ⁶

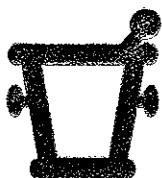


CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3-4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4,8-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			5
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5-6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5-6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5-6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	3

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	10-11
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	
13		14b Why the trial ended or was stopped	
14			
15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
17		by original assigned groups	
18			
19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
20	estimation	precision (such as 95% confidence interval)	
21		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
22	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	
23		pre-specified from exploratory	
24			
25	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
26			
27	Discussion		
28	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
29	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	
30	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
31			
32	Other information		
33	Registration	23 Registration number and name of trial registry	1-2
34	Protocol	24 Where the full trial protocol can be accessed, if available	
35	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	13
36			

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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DK-7100 Vejle	DK-6500 Vojens
Denmark	Denmark
<input type="checkbox"/> Tel.: +45 75 85 74 00	Fax: +45 75 85 74 74

Statement re. Clinical trial

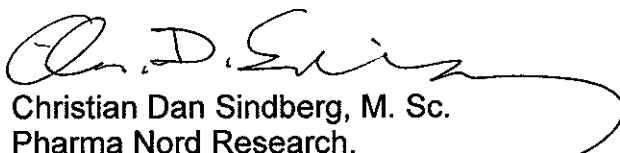
For the clinical trial

The effect of Melatonin on depression, anxiety, cognitive function and sleep disturbances in breast cancer patients,
ref no. MVH-03-MELODY
Eudract CT no 2010 -022460-12

conducted by

Melissa Voigt Hansen
Department of Surgical Gastroenterology
Herlev Hospital
Denmark

we hereby declare that the test preparations produced for the trial consists of verum and placebo tablets that has the exact similar physical appearance and cannot be distinguished by other means than analysis.


Christian Dan Sindberg, M. Sc.
Pharma Nord Research,
Vejle, December 13th 2011

PHARMA NORD APS
Sadelmagervej 30-32
7100 Vejle
Tlf. 75 85 74 00

Dep. QA/QC		Pharma Nord	Doc. no. L373-00-000
Prep. by K. Frederiksen			Ed nr. 1
Date 160611	Last ed. ----	Certificate of Analysis	
Auth. by A.Rishede		Product Bio-Melatonin 3 mg v. 1.2	Package Klinisk forsøg blistre

Product code:	373	
Batch no.:	1101654	
Bulk batch no.:	019860	
Date of Manufacture:	07.2010	
Expiry Date:	07.2013	
Storage:	Room temperature.	
Test/Assay:	Results:	Limits:
Appearance:	conforms	Clear coated white round biconvex tablet.
Size:	conforms	7.5 mm
Average weight:	143 mg	137.2-159.4 mg
Uniformity of mass:	conforms	Ph.Eur.
Mass Variation	conforms	Ph.Eur.
Disintegration:	1 min.	< 30 min, Ph.Eur.
Dissolution:	conforms	Q=75 % (45 min)
Identification:		
- Melatonin:	conforms	Conforms to standard, IR
- Melatonin:	conforms	Positive, HPLC
Assay:		
- Melatonin:	3.06 mg	2.85-3.15 mg, HPLC
Impurities:		
-NASE:	0.00 %	≤ 0.5 %
-SERO:	0.00 %	≤ 0.5 %
-DASE:	0.00 %	≤ 0.5 %
-MEXA:	0.00 %	≤ 0.5 %
-Each unknown:	0.00 %	≤ 0.5 %
-Total impurities:	0.00 %	≤ 0.5 %
Microbiological standard *:		
-Total viable aerobic count:	< 100 /g	< 10 ³ / g
-Fungi:	< 10 /g	< 10 ² / g
-E-coli:	neg. in 1 g	Neg. in 1 g

*: Assayed once a year. n.a not assayed.

It is hereby certified that the above batch is manufactured, controlled and released according to the principles of Good Manufacturing Practice.

160611 A.Rishede

QA-Department

Pharma Nord Aps, Vojens, Denmark

Dep. QA/QC		Pharma Nord	Doc. no. P373-90-000
Prep. by K. Frederiksen			Ed nr. 1
Date 160611	Last ed. ----	Certificate of Analysis	
Auth. by A.Rishede		Product Bio-Melatonin 3 mg v. 1.2 Placebo	Package Klinisk forsøg blistre

Product code: 373 (Placebo)

Batch no.: 1101655

Bulk batch no.: 116360

Date of Manufacture: 07.2010

Expiry Date: 07.2013

Storage: Room temperature.

Test/Assay:

Appearance:

Size:

Average weight:

Disintegration:

Assay*:

- Melatonin:

Microbiological standard :

-Total viable aerobic count:

-Fungi:

-E-coli:

Results:

conforms

conforms

143 mg

5 min.

N.d

< 100 /g

< 10 /g

neg. in 1 g

Limits:

Clear coated white round
biconvex tablet.

7.5 mm

137.2-159.4 mg

< 30 min, Ph.Eur.

Not detected

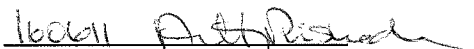
< 10³ / g

< 10² / g

Neg. in 1 g

*: N. d not detected.

It is hereby certified that the above batch is manufactured, controlled and released according to the principles of Good Manufacturing Practice.



QA-Department

Pharma Nord ApS, Vojens, Denmark