PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Melissa Voigt Hansen, Michael Tvilling Madsen, Ida Hageman, Lars Simon Rasmussen, Susanne Bokmand, Jacob Rosenberg, Ismail Gögenur

VERSION 1 - REVIEW

REVIEWER	Daniel P Cardinali MD PhD Director, Teaching & Research Faculty of Medical Sciences Pontificia Universidad Católica Argentina
REVIEW RETURNED	05/12/2011

GENERAL COMMENTS	This is a well designed protocol for a prospective double-blinded, randomized, placebo-controlled trial including 260 patients to investigate whether treatment with oral melatonin has a prophylactic or ameliorating effect on depressive symptoms, anxiety, sleep disturbances and cognitive dysfunction in patients with breast cancer. The clock-gene PER3 will be also measured. The assessment of primary, secondary and tertiary outcomes is clearly defined and the statistical approach employed is sound. My single concern deals with the melatonin dose to be employed (6 mg). Since melatonin has a short half life (less than 30 min) its efficacy in promoting and maintaining sleep has not been uniform in the studies undertaken so far. Thus the need for the development of prolonged release preparations of melatonin or of melatonin agonists with a longer duration of action on sleep regulatory structures in the brain arose. The novel melatonergic antidepressant agomelatine (Valdoxan, Servier) is an example. Agomelatine acts on both MT1 and MT2 melatonergic receptors with a similar affinity to that of melatonin; it also acts as an antagonist to 5-HT2C receptors at a 3 orders of magnitude greater concentration. Agomelatine has been licensed by EMEA for treatment of major depressive disorder at doses of 25 – 50 mg/day. As shown by the binding affinities, half-life and relative potency of agomelatine it is clear that studies using 6 mg melatonin/day may be unsuitable to give appropriate information on the native molecule´s antidepressant activity. As stated by the authors melatonin has a high safety profile and it is usually remarkably well tolerated. In some studies melatonin has been administered to patients at large doses (up to 300 mg/day). If one expects melatonin to be an effective antidepressant it is unlikely that the 6-mg dose of melatonin planned in this protocol will give useful information.

REVIEWER	Dr Richard S Bourne Consultant Pharmacist - Critical Care Sheffield Teaching Hospitals Northern General Hospital Herries Road Sheffield S5 7AU United Kingdom No competing interests declared
REVIEW RETURNED	06/12/2011

GENERAL COMMENTS	The MELODY trial The protocol and rationale of the randomised, placebo-controlled, double blind study are very well described. The study design overall is appropriate, including all sections such as the exclusion criteria which are evidence based. Major Comments: The sample size estimation is based on a conservative estimate of the incidence of depression of 30% and that this will be reduced to 15% with melatonin. The authors should add a reference to support their estimation that melatonin therapy will halve the incidence of depression. Actigraphy is stated to have “a high sensitivity and specificity for detecting sleep start, sleep periods and awakenings” (Ref 59). It has a lower specificity for sleep parameters compared to polysomnography. However, whilst the use of actigraphy is not recommended to routinely to evaluate sleep disorders, it may be used in the “assessment of sleep variability, measurement of treatment effects, and detection of sleep phase alterations in insomnia secondary to circadian rhythm disturbance” [Littner M, et al: Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. Sleep 2003, 26:337-41]. Whilst the use of actigraphy (supported by the use of sleep diaries) to quantify sleep parameters as described in this study is entirely appropriate, some acknowledgement of the caveats should be included. In the Discussion, the complications related to postoperative cognitive dysfunction (POCD) are identified. POCD in patients is known to be associated with increased long term cognitive dysfunction. However, the testing of cognitive function is only undertaken preoperatively and at 2 weeks and 3 months postoperatively. Therefore, the prevalence of immediate (in-hospital) POCD will not be reported. It will remain unknown whether any beneficial effect of melatonin therapy identified was related to reduction in immediate POCD, or even related to reduction in exposure to antipsychotic medication. The prevalence of delirium has implications for hospital resources and any intervention that is well tolerated and effective in the reduction of hospital POCD/ delirium is important. Melatonin supply will be from PharmaNord (Bio-melatonin®). If this is an unlicensed medication in the EU, a certificate of analysis should be requested for the melatonin tablet batches to confirm

	melatonin activity. A statement that the tablets (melatonin/ placebo) are physically identical should be included. Additional comments: Abstract "Minutes of sleep" [also in Table 2] and "sleep effectiveness" are referred to in the Abstract, whilst more correctly referred to in the Effect Parameters - Actigraphy subsection as "Total Sleep Time" and "Sleep Efficiency". Sleep hygiene advice should be provided to all patients. Other collected data: Consider the addition of the Anaesthetic regime if this will vary significantly between patients, as there are conflicting reports that this intervention may affect melatonin plasma levels postoperatively [e.g. Reber A, et al: General anaesthesia for surgery can influence circulating melatonin during daylight hours. Acta Anaesthesiol Scand 1998, 42:1050-1056 & Karkela J, et al: The influence of anaesthesia and surgery on the circadian rhythm of melatonin. Acta Anaesthesiol Scand 2002;46:30-36 & Gogenur I, et al: Disturbances in melatonin, cortisol and core body temperature rhythms after major surgery. World Journal of Surgery 2007, 31:290-298].

VERSION 1 – AUTHOR RESPONSE

Reviewer: Daniel P Cardinali MD PhD
Director, Teaching & Research
Faculty of Medical Sciences
Pontificia Universidad Católica Argentina

This is a well designed protocol for a prospective double-blinded, randomized, placebo-controlled trial including 260 patients to investigate whether treatment with oral melatonin has a prophylactic or ameliorating effect on depressive symptoms, anxiety, sleep disturbances and cognitive dysfunction in patients with breast cancer. The clock-gene PER3 will be also measured. The assessment of primary, secondary and tertiary outcomes is clearly defined and the statistical approach employed is sound.
My single concern deals with the melatonin dose to be employed (6 mg). Since melatonin has a short half life (less than 30 min) its efficacy in promoting and maintaining sleep has not been uniform in the studies undertaken so far. Thus the need for the development of prolonged release preparations of melatonin or of melatonin agonists with a longer duration of action on sleep regulatory structures in the brain arose. The novel melatonergic antidepressant agomelatine (Valdoxan, Servier) is an example. Agomelatine acts on both MT1 and MT2 melatonergic receptors with a similar affinity to that of melatonin; it also acts as an antagonist to 5-HT2C receptors at a 3 orders of magnitude greater concentration. Agomelatine has been licensed by EMEA for treatment of major depressive disorder at doses of 25 – 50 mg/day. As shown by the binding affinities, half-life and relative potency of agomelatine it is clear that studies using 6 mg melatonin/day may be unsuitable to give appropriate information on the native molecule´s antidepressant activity. As stated by the authors melatonin has a high safety profile and it is usually remarkably well tolerated. In some studies melatonin has been administered to patients at large doses (up to 300 mg/day). If one expects melatonin to be an effective antidepressant it is unlikely that the 6-mg dose of melatonin planned in this protocol will give useful information.

Firstly our aim is to test the prophylactic and/or ameliorating effect of melatonin on patients that are not on beforehand depressed or have depressive symptoms. To our knowledge no such studies exist.

Furthermore no comparative studies between agomelatine and melatonin exist. Only one study exists (Carman JS, Post Rm, Buswell R et al. Negative effects of melatonin on depression. Am J Psychiatry 1976;133:1181-1186) where the direct effect of melatonin on depression is tested and this study is from 1976 and only includes 6 patients with depression.
Not many trials of exogenous melatonin treatment in patients with depression have been completed since this preliminary study in 1976. In addition these few studies (deVries MW, Peeters FP. Melatonin as a therapeutic agent in the treatment of sleep disturbance in depression. J Nerv Ment Dis 1997;185:201-202, Leibenluft E, Feldman-Naim S, Turner EH et al. Effects of exogenous melatonin administration and withdrawal in five patients with rapid-cycling bipolar disorder. J Clin Psychiatry 1997;58:383-388, Dalton EJ, Rotondi D, Levitan RD et al. Use of slow-release melatonin in treatment-resistent depression. J Psychiatry Neurosci 2000;25:48-52, Dolberg OT, Hirschmann S, Grunhaus L. Melatonin for the treatment of sleep disturbances in major depressive disorder. Am J Psychiatry 1998;155:1119-1121), have many limitations such as; being a one-patient case, including very small populations of 5-19 patients, primarily testing the effect of melatonin on the sleep disturbances related to depression and hereby not the direct effect on depression as a primary outcome and giving the melatonin together with other antidepressants or psychotropic medications.
Our hypothesis of the possible antidepressant effect of melatonin is supported by several animal studies (Crupi R, Mazzon E, Marino A et al. Melatonin treatment mimics the antidepressant action in chronic corticosterone-treated mice. J Pineal Res 2010;49:123-129, Binfaré RW, Mantovani M, Budni J et al. Involvement of dopamine receptors in the antidepressant-like effect of melatonin in the tail suspension test. Eur J Pharmacol 2010;638:78-83, Raghavendra V, Kaur G, Kulkarni SK. Anti-depressant action of melatonin in chronic forced swimming-induced behavioural despair in mice, role of peripheral benzodiazepine receptor modulation. Eur Neuropsychopharmacol 2000;10:473-481, Kopp C, Vogel E, Rettori M-C et al. The effects of melatonin on the behavioural disturbances induced by chronic mild stress in C3H/He mice. Behav Pharmacol 1999;10:73-83).
Furthermore experimental animal studies on agomelatine have proven that the anti-depressant effect of agomelatine is blocked by the melatonin receptor antagonist S 22153 (Bertaina-Anglade V, Drieu la Rochelle C, Boyer P-A et al. Antidepressant-like effects of agomelatine (S 20098) in the learned helplessness model. Behav Pharmacol 2006;17:703-713, Papp M, Gruca P, Boyer P-A et al. Effect of agomelatine in the chronic mild stress model of depression in the rat. Neuropsychopharmacology 2003;28:694-703).
As mentioned in the protocol article a complex relationship exists between depression and breast cancer with the influence of many factors. Another aspect in our study is the possible secondary gain/indirect effect on depression/depressive symptoms which can be achieved by improving sleep, cognitive function and anxiety through melatonin treatment.
Last, but not least, the local ethics committee in Denmark would not accept this trial with a higher dose than the planned 6 mg.

Reviewer: Dr Richard S Bourne
Consultant Pharmacist - Critical Care

Sheffield Teaching Hospitals
Northern General Hospital
Herries Road
Sheffield
S5 7AU
United Kingdom

No competing interests declared

The MELODY trial

The protocol and rationale of the randomised, placebo-controlled, double blind study are very well described. The study design overall is appropriate, including all sections such as the exclusion criteria which are evidence based.

Major Comments:

The sample size estimation is based on a conservative estimate of the incidence of depression of 30% and that this will be reduced to 15% with melatonin. The authors should add a reference to support their estimation that melatonin therapy will halve the incidence of depression.

A specific reference is not found to support this as no previous studies have been completed. As mentioned in the protocol numerous studies have demonstrated the importance of depression, anxiety, sleep disturbances and cogntive disturbances in patients with breast cancer (ref. 7,9,10,12,68,76,89,90,91,92,100,101). As the exact mechanism behind the development of depression in this group of patients is not known, we have based our estimate that melatonin therapy will halve the incidence of depression on the effect of melatonin on anxiety, sleep disturbances and the effect of melatonin receptor agonists on depression.

Actigraphy is stated to have “a high sensitivity and specificity for detecting sleep start, sleep periods and awakenings” (Ref 59). It has a lower specificity for sleep parameters compared to polysomnography. However, whilst the use of actigraphy is not recommended to routinely to evaluate sleep disorders, it may be used in the “assessment of sleep variability, measurement of treatment effects, and detection of sleep phase alterations in insomnia secondary to circadian rhythm disturbance” [Littner M, et al: Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. Sleep 2003, 26:337-41]. Whilst the use of actigraphy (supported by the use of sleep diaries) to quantify sleep parameters as described in this study is entirely appropriate, some acknowledgement of the caveats should be included.

The following has been added to the section about actigraphy:
“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.”

In the Discussion, the complications related to postoperative cognitive dysfunction (POCD) are identified. POCD in patients is known to be associated with increased long term cognitive dysfunction. However, the testing of cognitive function is only undertaken preoperatively and at 2 weeks and 3 months postoperatively. Therefore, the prevalence of immediate (in-hospital) POCD will not be reported. It will remain unknown whether any beneficial effect of melatonin therapy identified was related to reduction in immediate POCD, or even related to reduction in exposure to antipsychotic medication. The prevalence of delirium has implications for hospital resources and any intervention that is well tolerated and effective in the reduction of hospital POCD/ delirium is important.

Firstly, in-hospital-delirium and the use of antipsychotic medication is not a significant problem in patients undergoing surgery for breast cancer, hence why we have not focused on this aspect at all. Secondly, we decided to focus our cognitive testing 14 days after surgery, as at this time the surgical stress phase is over and patients have been resuming their daily activities, which we find more clinically relevant than the immediate reduction in POCD.

Melatonin supply will be from PharmaNord (Bio-melatonin®). If this is an unlicensed medication in the EU, a certificate of analysis should be requested for the melatonin tablet batches to confirm melatonin activity. A statement that the tablets (melatonin/ placebo) are physically identical should be included.

As Bio-melatonin is only licensed in Hungary and therefore unlicensed in the rest of the EU countries we have attached a certificate of analysis. Furthermore a statement regarding the appearance of the melatonin/placebo tablets is also attached.
The following has been added under study design and objectives: “The melatonin/placebo supply will be from Pharma Nord ApS, Vejle, Denmark and the tablets (melatonin/placebo) are physically identical.

Additional comments:
Abstract
“Minutes of sleep” [also in Table 2] and “sleep effectiveness” are referred to in the Abstract, whilst more correctly referred to in the Effect Parameters - Actigraphy subsection as “Total Sleep Time” and “Sleep Efficiency”.

Appropriate changes have been made in the abstract and in table 2.

Sleep hygiene advice should be provided to all patients.

No extra sleep hygiene advice is provided as this could influence our outcome, so we are not able to distinguish between the effects of the medication or the advice. Furthermore to make the results more clinically relevant we opted against giving sleep hygiene advice as this is not part of the routine in the department.

Other collected data:
Consider the addition of the Anaesthetic regime if this will vary significantly between patients, as there are conflicting reports that this intervention may affect melatonin plasma levels postoperatively [e.g. Reber A, et al: General anaesthesia for surgery can I nfluence circulating melatonin during daylight hours. Acta Anaesthesiol Scand 1998, 42:1050-1056 & Karkela J, et al: The influence of anaesthesia and surgery on the circadian rhythm of melatonin. Acta Anaesthesiol Scand 2002;46:30-36 & Gogenur I, et al: Disturbances in melatonin, cortisol and core body temperature rhythms after major surgery. World Journal of Surgery 2007, 31:290-298].

Firstly, studies in respect to the anaesthetics regimes have shown that these disturbances in endogenous melatonin plasma levels postoperatively only occur in the first few postoperative days. Since we give melatonin in supraphysiological doses over a period of app. 13 weeks we do not expect that this slight, short difference, if any, will have any contribution. In addition, the anaesthetic regime is carefully standardised as all patients receive total intravenous anaesthesia using propofol and fentanyl.

VERSION 2 – REVIEW

REVIEWER	Daniel P Cardinali MD PhD Director, Teaching & Research Faculty of Medical Sciences Pontificia Universidad Católica Argentina
REVIEW RETURNED	18/12/2011

The reviewer completed the checklist but made no further comments.