A Randomized Double Blind Placebo Controlled Trial of Ramelteon in the Prevention of Postoperative Delirium in Older Patients Undergoing Orthopedic Surgery: The RECOVER Study

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Study Protocol and Statistical Plan

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RECOVER STUDY Protocol

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Postoperative delirium, an acute confusional state caused by an underlying physiological disturbance following surgery and characterized by sleep/wake cycle disturbances, [1]is a serious public health problem that disproportionately affects older people. [2,3]Delirium is associated with many negative outcomes including: increased mortality, longer hospital stays, increased institutionalization after acute care hospitalization, worse cognitive and physical outcomes (both short- and long-term), and significant distress for patients and their families. [4-9]Costs to the healthcare system due to all episodes of delirium among the elderly range from $38 to $152 billion/year. [10,11]Aging of the population means increasing numbers of older adults are undergoing surgery – making postoperative delirium prevention an urgent priority. [12]

The mechanisms leading to postoperative delirium are unclear, though delirium is almost always accompanied by symptoms of sleep-wake disturbance, such as daytime somnolence and nighttime sleeplessness. [13-16] Diurnal dysregulation may be causally important in the genesis of delirium, and melatonin agonists may prevent delirium by maintaining the circadian rhythm. [17] The rationale for using a melatonin agonist is further strengthened by multiple biological effects on neuro-inflammatory mechanisms implicated in delirium, [18-20]via antioxidant and possibly anti-amyloid effects. [21-23] Reports from a recent single-blind randomized controlled trial (RCT) of ramelteon in a related but non-generalizable older-aged medically ill patient population suggest a significant reduction in new onset delirium (30% of placebo-treated vs. 3% of ramelteon-treated; effect size of 0.85). [24]

We propose a proof-of-concept (phase 2) double-blind randomized placebo-controlled trial to evaluate the efficacy and short-term safety of ramelteon for the prevention of postoperative delirium in a high-risk group of patients, 65 years and older, with MMSE[25] scores $\geq$ 15, planned orthopedic surgery. Our prior work demonstrates the feasibility of conducting a prevention trial in this population, using state-of-the-art delirium detection and diagnosis methodology. [5,25] Should this preliminary trial, show evidence of efficacy and adequate safety, then a phase 3 trial will be proposed.

Our group has demonstrated that an early predictor of subsequent delirium is the presence of delirium immediately upon recovery from general anesthesia in the post anesthesia care unit (PACU). [5,26,27]The proposed trial will incorporate assessment of PACU delirium as a means of early delirium detection in helping to determine the efficacy of the ramelteon intervention.

2. Objectives (include all primary and secondary objectives)

The proposed trial will involve administering 8 mg ramelteon orally (1 dose preoperatively and 2 doses postoperatively) or placebo in 80 older-aged patients to test the following:

Specific Aim 1 (primary outcome): To compare delirium incidence and severity between ramelteon and placebo using the DSM 5 criteria by expert panel consensus.

Hypothesis 1: Compared to placebo, ramelteon will be associated with a) a lower incidence and severity of postoperative delirium immediately upon recovery from anesthesia in the PACU, and b) with a lower incidence and severity of delirium on postoperative day (POD) 1 and POD 2.

Specific Aim 2 (safety outcome): To compare adverse events (AEs) and serious adverse events (SAEs) between ramelteon and placebo.

Hypothesis 2: Ramelteon will have an adequate safety profile in this postoperative cohort, sufficient to support conducting a larger prevention trial. Specifically, compared to placebo, ramelteon will not be associated with increased incidence of postoperative delirium or with increased adverse side effects including fatigue, headache and next day somnolence during the treatment episode.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

a. Significance:

a.1. Overview: Postoperative delirium in older adults is frequent, associated with poor outcomes, and a serious public health problem. Delirium, or an acute confusional state caused by an underlying physiological disturbance, [1] occurs in up to 60% of older patients undergoing major surgery.[12, 27-30] It is associated with increased mortality, morbidity, cognitive impairment, functional decline, institutionalization following acute care hospitalization, and psychological distress for patients and their families.[5-9] Healthcare costs due to all episodes of delirium in the elderly range from $38 to $152 billion/year.[10,11] Older age and impaired cognition prior to surgery are risk factors for postoperative delirium. [31,32] For many older patients, a postoperative delirium can tip the balance and result in significant reductions in independence and function. [33]

a.2. Delirium: A syndrome characterized by a circadian rhythm disturbance. Disrupted sleep-wake cycle occurs in 73-80% of patients with delirium and includes day/night reversal and fragmentation.[14,16] Motor activity during a delirious episode is also frequently inappropriate in its timing – with daytime somnolence and nighttime hyperactivity, suggesting circadian dysfunction as a possible central mechanism in delirium.[13,15] The relationship may be bidirectional: sleep deprivation may lead to significant cognitive deficits and may itself cause or worsen delirium. [13,34,35] Sleep/wake cycle disruption is central to postoperative delirium.

a.3. Melatonin: A critical modulator of circadian rhythm that decreases with age. Melatonin is secreted by the pineal gland in response to the suprachiasmatic nucleus (SCN) in the hypothalamus, which contains a free running circadian pacemaker and is also entrained by neural input from the retina where photoreceptors are stimulated by darkness and inhibited by light. Noradrenergic photoreceptors synapse in the SCN, stimulating fibers that travel to the superior cervical ganglion and return to the pineal gland where production of melatonin occurs, from its precursor, serotonin. Melatonin levels peak in the evening and night hours with a 24-hour periodicity. [36-38] In healthy young adults the daytime/nighttime peak values are 10/60 pg/mL, respectively. Melatonin production peaks in young children and falls over the course of the lifespan. [37] Serum melatonin levels are significantly lower, with delayed peak values in older subjects with insomnia compared to age-matched controls. Older individuals have decreased nocturnal pineal melatonin synthesis, thought to be secondary to neurodegeneration. [39]

a.4. Melatonin: Additional neuroprotective effects via antioxidant activity at high doses. When administered at 10-100 times the physiologic dose (3-30 mg orally), melatonin exerts cell protection through antioxidant activities, modulates the immune system, and supports mitochondrial function. [21] It acts via cellular membrane G protein-coupled melatonin receptors MT1 and MT2 throughout the human brain, including microglia in the cortex and brainstem, and in

the periphery in cell types such as lymphocytes, bone marrow, gut and retina. Receptor stimulation enhances antioxidant potential of the cell by increasing enzyme and mitochondrial ATP synthesis. [40] Animal models have demonstrated the protective effects of melatonin after ischemic and reperfusion injury of liver, heart and brain. [41-46] Evidence suggests that melatonin might be a rational treatment for cerebral edema due to blood brain barrier protection. [47-49] Melatonin also protects against Aβ-mediated toxicity and attenuates Alzheimer-like tau hyperphosphorylation. [22,23]

a.5. Pathophysiology of Delirium: Neuroinflammation and neurotransmitter dysregulation are implicated as possible mechanisms causing delirium, particularly in response to stress and inflammation of surgical procedures and the direct effects of anesthetic agents. [13,50-52] Impaired cerebral oxidative metabolism resulting in increased dopaminergic, noradrenergic and glutamatergic activity and decreases in cholinergic activity is hypothesized to cause delirium. [18,19,35,52,53] Melatonin blocks dopamine release from the hypothalamus in animal models. Melatonin agonists may have beneficial effects in delirium prevention through: 1) maintenance of sleep and diurnal rhythms, 2) anti-inflammatory effects, and/or 3) dopamine blockade.

a.6. Low Postoperative Serum Melatonin: Associated with delirium. Melatonin levels have been reported to be low on the first night following surgery, returning to normal in subsequent days when measured in young women following gynecologic procedures. [54] Inpatients developing delirium after undergoing major abdominal surgery without life-threatening postoperative complications had lower serum melatonin levels compared to preoperative baseline; no such change was evident in patients who did not develop delirium. [55] Although absolute preoperative levels of melatonin were similar in an observational study of older patients undergoing major surgery, patients who developed postoperative delirium demonstrated significantly lower serum melatonin concentration at 1 hour after surgery compared to those who remained delirium free. [56] Postoperative delirium, without life-threatening complications, is associated with lower melatonin levels immediately following surgical procedures.

a.7. Exogenous Melatonin and Delirium Prevention: findings are mixed. Two trials in postoperative patients used superphysiologic doses: the first using 7.5 mg melatonin orally the night prior to, and a second dose 90 minutes before surgery. Active treatment was compared to patients receiving two other agents or no drug at all. A placebo was not used. The new occurrence of delirium on days 0-3 in the groups with no drug treatment vs. melatonin was 33% vs. 9%, respectively. [57] The second was a recently published placebo-controlled RCT, testing oral doses of 3 mg of melatonin, administered for 5 consecutive nights in 378 older patients (mean age 84 years) undergoing hip fracture repair. This trial demonstrated neither delirium preventive effect (55/186 or 30% among melatonin group vs. 49/192 or 26% in the placebo) nor any functional differences at 3 months. [58] Secondary analysis revealed that patients treated with melatonin, had fewer episodes of delirium lasting longer than 2 days, compared to placebo. [58] Another placebo-controlled RCT was conducted in a medically ill patient population aged 65 and older using a physiologic dose of 0.5 mg of melatonin at bedtime for up to 14 days during a medical hospitalization. [59] The delirium prevalence in placebo vs. melatonin (31% vs.12% respectively; $p<0.02$) resulted in an absolute risk reduction of 15.6% (NNT = 6.4).

a.8. Advantages of Ramelteon – include quality control and longer drug effect. Unlike melatonin, which is considered a dietary supplement, ramelteon is an FDA-regulated pharmaceutical. Inadequate comparability of biologic availability of melatonin, between different manufacturers and even between batches from the same company, has been cited as a major barrier to studying the effects of exogenous melatonin in clinical trials. [36] As a regulated drug, ramelteon,

has distinct advantages with respect to quality control and comparable melatonergic activity. Furthermore a biologically active metabolite M-II contributes to a longer total drug effect of 5 hours compared to 1- 2 hours for melatonin. [39,60]

a.9.Ramelteon and Delirium Prevention: Promising in medically ill patients. A trial employing ramelteon in a delirium prevention study of 67 medically ill patients, > 65 years of age demonstrated a significant reduction in delirium in ramelteon-treated vs. placebo (3% vs. 32% respectively; p = 0.003) reflecting a relative risk (RR) of 0.09 (95% CI 0.01-0.69).24 Of 1,126 patients screened, 101 met inclusion criteria. Exclusions included a length of hospital stay or life expectancy < 48 hours, diagnosis of 1) liver failure, 2) Dementia with Lewy Bodies, 3) alcohol dependency, 4) psychotic disorder, 5) bipolar disorder, or 6) prior use of fluvoxamine. Outcome measures were DSM –IV [61] based delirium diagnosis and DRS-98R [62] as assessed by study psychiatrists. The intervention and control groups were balanced regarding important confounders: patients were comparable in baseline demographics, levels of baseline dementia and severity of illness. No one stopped the ramelteon due to adverse outcomes. The most significant risk of bias was due to a non-identical appearing placebo, potentially leading to unmasking of treatment assignment.

a.10. Summary of Significance: Sleep disruption is a central feature of delirium, and preliminary data suggests that melatonin deficiency is associated with postoperative delirium in older adults. The use of ramelteon as a melatonin agonist perioperatively could prevent delirium by a number of mechanisms including enhancing circadian rhythm and promoting sleep, direct antioxidant and anti-inflammatory activity and central dopamine blockade. While results of melatonin RCTs have been quite mixed, ramelteon offers pharmacokinetic and pharmacodynamic advantages over melatonin that may enhance potential benefits. Successful prevention of postoperative delirium will result in improvements in the lives of older patients undergoing surgery and significant cost-savings to the healthcare system.

b. Innovation:

b.1. Melatonergic agents - a safer alternative for delirium prevention: Previous delirium prevention trials have tested pharmacologic agents that directly increase cholinergic, or decrease dopaminergic activity. Rivastigmine, a cholinesterase inhibitor, was discontinued mid-study due to concern for increased mortality in the treatment group. [63] Dopamine-blocking antipsychotic agents (i.e. haloperidol) have not demonstrated any treatment or prevention benefit for delirium in critically ill adults. [64,65] Results of dopamine blocking agents in prevention trials in older-aged postoperative samples are mixed: antipsychotics may hold some promise [66] but are complicated by the increased risk of stroke and sudden death, particularly with long-term use in patients with dementia, making this a high-risk strategy for the highest risk patients. [67-69] Safer delirium pharmacologic prevention strategies are needed. Ramelteon, as a melatonin agonist, may have a more benign side-effect profile in older people and is approved currently as a sleep aide. [39,70,71]

b.2. A Different High-Risk Population reflecting "real-world" surgical patients: Ramelteon has not yet been used as a delirium-prevention agent in a postoperative population which includes persons with significant cognitive impairment. Our group has expertise early delirium evaluation following recovery from anesthesia on the day of surgery in addition to assessments on postoperative days. This first study of ramelteon in an older postoperative patient population inclusive of those with preoperative cognitive impairment will use the innovative approach of early delirium detection to study the evolution of the syndrome in the immediate recovery period and on subsequent postoperative days.

b.3. A Rigorously Conducted RCT Ensuring Adherence: A trial that includes complete masking of study drug/placebo and ensures adherence to first dose through testing for a tracer substance will represent a unique contribution to scientific knowledge. Rigor is needed to demonstrate that delirium prevention effects are due to ramelteon, particularly before designing more expensive phase 3 trials. A rigorously conducted RCT will identify the potential for ramelteon to prevent delirium in a postoperative population.

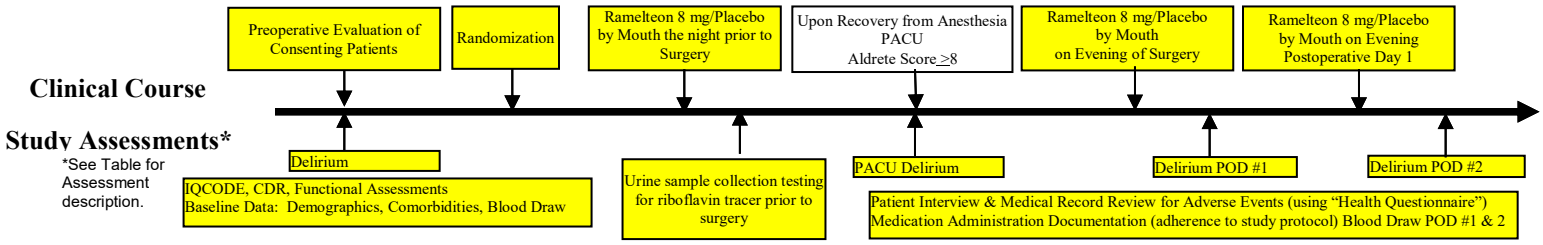
b.4. Summary of Innovation: This exploratory study is a novel approach to preventing postoperative delirium in older patients with and without cognitive impairment – a condition for which there is no prevention and little translational inquiry. Older individuals undergoing surgery, do so in the hopes of improving quality of life. Delirium prevention following surgery will significantly improve independence, well-being and decrease institutionalization. A widely available, generally safe intervention (ramelteon) would be exciting, novel, guiding translational inquiry to test important new mechanistic models of postoperative delirium.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Overview: This randomized, masked, controlled trial is designed to evaluate the short-term safety and efficacy of peri-operative, orally administered 8 mg of ramelteon for the prevention of postoperative delirium; 80 delirium-free participants (n=40 per arm) ≥ 65 years of age, infection free and undergoing orthopedic surgery and post-procedure inpatient admission, will be randomized to ramelteon/placebo at the preoperative study visit, with administration of 3 nightly doses: one preoperatively and two following surgery while monitoring incidence of postoperative delirium. The following diagram outlines the proposed study timeline. All activities outlined in yellow indicate research activities while white background indicates routine clinical care.

Timeline of Clinical Course and Study Assessment (not to scale)



Choice of dosing times: include three consecutive evenings: 1) prior to surgery, 2) the night of surgery or POD 0 and 3) POD 1. The preoperative administration of ramelteon is designed to correct melatonergic deficiencies observed immediately following surgery and to enhance circadian rhythm and sleep effects. [54] Participants who are admitted to hospital the night before surgery will have study assigned medication administered by clinical staff, similar to the procedure for POD 0 and POD 1 doses. Participants undergoing elective surgery are given the first dose of medication at their preoperative study visit with instructions to take it the night before surgery. Study personnel will contact to remind the participant. Lack of adherence to self-administration of medication has been described as a barrier in the literature. [72] Serving as a biologic tracer, 100 mg of riboflavin (Vitamin B_2) will be added to both the active agent and placebo of doses to be self-administered

outside of the hospital. Since riboflavin fluoresces under UV light, a urine sample obtained in the OR at the time of catheterization, will be sent for quantitative fluoroscopy using a cutoff of > 900 ng/ml as evidence of adherence. Replacement recruitment will be completed for any participants with urine samples negative for riboflavin.

Choice of study population and outcome measurement time points: Delirium, diagnosed early in recovery from anesthesia, is very common in older adults (45% after recovery from general anesthesia) and predicts delirium in the subsequent postoperative course. [5,26,27,73]This finding runs contrary to the view that postoperative delirium cannot be diagnosed unless a period of lucidity has occurred following recovery from anesthesia, and that commonly observed confusion and uncooperativeness upon recovery are benign emergence phenomena. [74] Since **our previous work suggests that the syndrome, regardless of its attribution, predicts delirium in the days following surgery as well as measurable changes in cognitive function**, [5] we have included two time periods of delirium incidence as our primary outcome: 1) in the PACU after recovery of arousal, hemodynamic, and respiratory function after anesthesia, as measured by Aldrete score $\geq$ 8;[74] and 2) during POD 1 and 2 independent of status in the PACU. This will allow for the study of preoperative ramelteon on immediate recovery and during the traditionally described delirium incidence in the days following surgery. For participants who discharge early from the hospital (prior to POD 2), delirium assessment will be conducted via telephone. While longer-term follow-up beyond POD 2 is desirable, it is difficult to complete in all patients in this preliminary study due to an institutional trend toward early post-surgery discharge. We plan to recruit patients with significant cognitive impairment at baseline (mild to moderate dementia) by including participants with Mini Mental State Exam (MMSE) scores $\geq$ 15. [75]Based upon our previous work, distribution of MMSE scores of 24-30, 15-23, and < 15 prior to surgery for this population will be 50-60%, 25-33% and 7-25% respectively. Participants who score below this cut-off are increasingly difficult to test, making delirium diagnosis difficult.

Randomization*:* A statistician (JML) will be responsible for design, implementation, and maintenance of randomization procedures that assign participants to active pharmaceutical or placebo. Since preoperative cognitive impairment is consistently and strongly associated with the development of postoperative delirium, our randomization process will stratify by preoperative MMSE exam score to ensure balanced allocation (MMSE score 24/30 - 30/30 and 15/30 - 23/30). Under supervision of the statistician, research pharmacy staff who have no contact with the patient or clinical staff will randomize participants using a computer program, utilizing dynamic allocation probabilities to balance the two groups on the dichotomous MMSE variable.

Masking Procedures*:* The research pharmacy staff will prepare the active treatment (ramelteon 8 mg) and placebo using identical gel caps containing 100 mg riboflavin for doses to be self-administered outside of the hospital. No riboflavin will be added to study doses to be administered by hospital nursing staff. Once randomized, the assigned agent will be labeled with the patient's name and medical record number with the administration instructions consistent with hospital policy. No markings will indicate identity of the agent. Participants admitted on the day of surgery will receive the assigned study medication (active treatment/placebo) at the study visit prior to surgery. For all inpatient doses clinical nursing staff will administer medication each evening (8-10 pm). Administration will be documented in the clinical electronic medication record and adherence closely monitored by research staff.

Concomitant Medications: All medications except those enumerated in exclusions will be allowed.[60]

Choice of Clinical Site and Feasibility of Recruitment: A total of 198 infection-free inpatients ≥ 65 years of age, underwent total hip or knee arthroplasty or revision under general anesthesia between 01/01/14-12/31/14 at JHBMC. The median (IQR) ASA physical status score and median surgical duration (IQR) was 3 (3-3) and 172 (122-216) mins. respectively, reflecting significant comorbidity and lengthy surgical times, consistent with high postoperative delirium risk likely to be at least 30%. [58]

b. Study duration and number of study visits required of research participants.

The study will include baseline data gathering prior to surgery and last for three days during admission to hospital for orthopedic surgery. The participants in this study will be invited to come to a hospital-based in-person preoperative study visit to obtain consent for the study, collect baseline data, including 5 ml (1 teaspoon) of blood draw for biomarkers and a baseline delirium assessment. If the patient is unable or unwilling to come to the hospital prior to surgery, study staff will offer to come to see the patient in the community such as in their home (if located within the vicinity of JHBMC and the patient is willing). If the patient lives out of state, or too far to allow study team travel, but still expresses interest in the study, the consent will be sent via email (from the secure JHMI server) or via fax after discussing the study with one of the provider staff by telephone. Baseline information that can be completed by phone will be obtained and remaining variables and blood draw will be completed in the morning of the day of surgery. Following randomization, study medication will be sent by courier or mail.

The patient will be asked to take the study medication (either ramelteon or placebo - both containing riboflavin) the night before surgery. For many patients this will occur at home prior to admission and research personnel will place telephone calls to ensure adherence by the patient. While in the hospital the patient will have a urine sample collected and sent on the day of surgery to test for riboflavin, will be visited by study staff to do a delirium assessment in the PACU upon recovery from anesthesia, and on two subsequent postoperative days. Two doses of the study drug will be prepared by the research pharmacy and administered by the patient's nurse. Blood will be drawn for biomarkers on POD1 and POD2. For the biomarker collection on POD1 and POD2, 5 ml (1 teaspoon) of blood will be collected during routine AM blood draw, and therefore will not involve an additional needle stick. If the participant is discharged from the hospital early (prior to POD2), the biomarker collection for that day will not be completed. For participants who are discharged from the hospital on postoperative day 0 or day 1, the remaining doses of study medication will be packaged by the pharmacy and given to the participant to take at place of discharge with instructions to take the medication at hour of sleep. Study staff will call the participant and complete the study questionnaires each day by telephone should the patient be discharged prior to postoperative day 2.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Blinding of study staff, clinical staff and the patient is critical for the design and the study aims – which seek to test whether ramelteon might prevent the development of postoperative delirium.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants will receive routine surgical and postoperative care. The study seeks to add exposure to ramelteon or placebo to test whether this intervention might decrease delirium - a common complication that occurs in the postoperative setting in older adults. No current therapy will be stopped.

e. Justification for inclusion of a placebo or non-treatment group.

The inclusion of a placebo treatment is critical in helping advance our understanding of the effects (both positive and negative) of ramelteon exposure. Placebo comparison is the only way that we can understand what is likely due to ramelteon and what is not.

f. Definition of treatment failure or participant removal criteria.

All consented participants will be retained in the study. Participants with no evidence of riboflavin in the urine sample as tested by fluorescence prior to surgery (i.e. evidence of non-adherence to the first dose of study agent) will continue in the study, receiving second and third doses of study agent, and undergoing delirium outcome measures at all time points; however recruitment will continue until 80 participants with documented adherence to the first doses of study agent is attained. Primary analysis will be intent to treat with all randomized subjects included in the analysis; secondary analysis will include only patients with documented adherence all 3 doses of study medication (a per protocol analysis).

Participants who have their surgery canceled after they have been randomized and who are likely to have surgery in the future will be considered “suspended” from the study. These participants will continue in their assigned condition. A new baseline will be completed prior to their new surgery date to establish that they continue to meet inclusion criteria. The team will proceed with the protocol pre- and postoperatively as assigned during the original randomization. If the participant takes any of the study medication prior to the original surgery, a minimum of 7 days between initial study dosing and the re-initiation of the protocol is required to ensure sufficient time to wash out. If the rescheduled surgery occurs less than 7 days after original dosing, the participant will be excluded from the study.

g. Description of what happens to participants receiving therapy when study ends or if a participant’s participation in the study ends prematurely.

Patients will be thanked for their help with the study and will be advised to call the PI with any questions.

5. Inclusion/Exclusion Criteria

Participants and Recruitment: Eligible patients at JHBMC, identified from the surgical scheduling roster (after obtaining HIPAA waiver) and/or from referral by the patient's surgeon will be approached. Upon receiving informed consent from the patient or their legally authorized representative (LAR), a MMSE [75] and delirium assessment (see below) will determine eligibility. A similar recruitment procedure is employed in the ongoing STRIDE study at the JHBMC. Both elective and emergency surgeries will be eligible. Recruitment of ethnic and racial minority participants will be a priority.

Inclusion Criteria: 1) Planned orthopedic surgery and inpatient stay following surgery; 2) Age $\geq$ 65 years; 3) MMSE $\geq$ 15 before surgery; 4) Can understand, speak, read and write English.

Exclusion Criteria: 1) Delirium diagnosis by Confusion Assessment Method [76](CAM) at baseline; 2) Unable to give informed consent (as tested for with the consent questionnaire during telephone screening and during baseline visit) due to cognitive impairment and a suitable LAR cannot be identified; 3) Declines participation; 4) Current medications that include: a) ramelteon, b) melatonin, c) fluvoxamine, d) rifampin, e) ketoconazole, or f) fluconazole; 5) History of ramelteon or riboflavin intolerance; 6) Heavy daily alcohol intake by medical record or history 7) Current moderate to severe liver failure (as defined by Charlson criteria[82]); 8) Evidence of Systemic Inflammatory Response Syndrome (SIRS) as measured by $\geq$ 2 criteria; [77] or 9) Presence of a condition that in the opinion of the PI might compromise patient safety if enrolled in the study.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Choice of agent and dose: Ramelteon is fast in onset. In a study of its safety and efficacy in older adults with chronic primary insomnia, using a two night crossover double-blind randomized controlled design, 8 mg of ramelteon demonstrated statistically significant decreases in sleep latency, increased sleep efficiency, and total sleep time compared to placebo as measured by polysomnography. [78]A 'first night' model of transient insomnia in 289 patients, naïve to a sleep laboratory environment and without any prior sleep difficulties, demonstrated similar findings with exposure to one dose. [71] Increased side effects, including fatigue, headache, and next-day somnolence, were experienced with 16 mg vs 8 mg, with no additional sleep architecture benefit. [60] Ramelteon (8 mg dose) is rapidly absorbed with peak serum concentrations at 1 hour and results in 20 -30 times the equivalent of nocturnal plasma melatonin levels. Such superphysiologic dosing may confer additional melatonergic neuroprotective benefits. Easily absorbed and highly protein bound, ramelteon is subject to extensive first pass metabolism, and rapidly eliminated ($t_{1/2}$ =1-2.6 hours). However the M II metabolite is highly biologically active, binding to both melatonin and serotonin-2B receptors. Elderly individuals metabolize ramelteon less rapidly than younger subjects, resulting in a doubling of exposure, given the same dose. [60,79] **Use of 8 mg of ramelteon in this protocol should confer both sleep promoting and circadian rhythm maintenance, and is a sufficient dose to provide superphysiologic melatonin receptor stimulation potentially consistent with antioxidant effects at a dose with relatively few side effects.**

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

An FDA waiver of need for IND was received on January 5th 2015 (see attached letter rejecting application for IND). One of the reasons given by the FDA was that the "investigation does not involve a change in route of administration, dosage or population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with the use of the drug product."

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. – Not applicable.

7. Study Statistics

a. Primary outcome variables.

Outcome Measure Specific Aim I – State-of-the-Art Delirium Assessment and Diagnosis: Well-trained research staff will conduct delirium assessments at baseline, to exclude cases of prevalent delirium, and at three later time points (see Figure and Table). This assessment includes: (1) face to face standardized interview of the patient regarding experiences, (2) standardized cognitive testing including the MMSE [75] and the abbreviated Digit Span, [80](3) history from family/friends familiar with the patient's cognitive baseline, (4) interview of nursing and other medical staff caring for the patient, and (5) review of medical records for evidence of behavioral disturbances and symptoms in previous 24 hours. Information on sleep disturbance is sought from all sources and is a symptom of delirium. Assessors will rate the CAM [81] and the Delirium Rating Scale-Revised '98 (DRS-R98) [62] for the prior 24 hours and describe the patient's behavior and mental state in a written narrative. If a patient is intubated the CAM-ICU [82] will be administered to determine delirium status. Patients who are comatose will be documented as such. (Preliminary data suggests that this is a rare occurrence <1%) Final adjudication of delirium diagnosis is derived after all data is presented to a panel of expert delirium diagnosticians (KN, PR and EO).

The primary diagnosis of delirium is based upon meeting all DSM-5 criteria (see appendix), and is determined by consensus of the expert panel - a method currently employed by this group of co-investigators in the STRIDE study.

A second outcome measure will be analyzed using the continuous variable of delirium severity derived from the DRS-98R severity measure.

Outcome Measure Specific Aim II- Adverse Events: All adverse events (AE and SAE) will be collected from the medical record and daily patient assessment using a customized instrument ("Health Questionnaire") which will systematically probe for known side effects (fatigue, headache and next day somnolence) (see Protection of Human Subjects).*Assessment of Outcome and Covariates:*

Table: Timing and Content of Patient Assessments

Assessments	Administration	Collection Instrument and Source
Cognition	Preoperative, PACU POD 1 and 2	Mini Mental State Exam Abbreviated Digit Span: Forwards and Backwards
Delirium	Preoperative, PACU, POD 1 and 2	CAM (full)[83] after patient exam + proxy/medical record review or CAM-ICU if intubated; DRS-98R (severity measure)
Dementia Rating	Preoperative	IQCODE from Proxy Interview; CDR based on Testing and Patient Interview
Age/sex/ race/occupational and education	Preoperative	Data Collection from based on Chart Review and Patient/Proxy Interview
Activities of Daily Living (ADL); Instrumental ADL	Preoperative	Katz and Lawton Scales from Patient and Proxy Interviews; Frailty Measure: Modified Fried Criteria
Comorbidities and review of sleep	Preoperative/POD 1 and	Charlson Index from Chart review, ASA score;

patterns;	POD 2	Pittsburgh Sleep Quality Index (baseline); Richards Campbell Sleep Questionnaire (POD 1 and 2)
Blood sample (5 ml)	Preoperatively, POD 1 and 2	Testing for the following inflammatory biomarkers: CRP (all testing will be performed by a research laboratory)
Medication administration (study agents), OR record/hospital course/discharge	Preoperative, PACU, POD 1 and 2	Data Collection based on Chart Review
Adverse events	PACU, POD 1 and 2	SAE + AE Custom-made Data Collection Forms ("Health Questionnaire") from Patient Interview and Records

b. Secondary outcome variables.

Baseline Covariate Measures:
Dementia Assessments: To measure the preoperative cognitive function, 1) patient interview and testing and 2) Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [83] completed at baseline after interview of a proxy informant, will inform rating of the 6 domains of the Clinical Dementia Rating (CDR) [84] by the delirium assessor. Evidence for the CDR ratings will be adjudicated by the consensus panel.
Other Baseline Covariates: Demographics, Activities of Daily Living (ADL's), [85,86] Instrumental ADL's (IADL's), [87] validated measures of medical comorbidity and severity (Charlson Comorbidity Index, [88] and ASA physical status classification system [89]), and a validated measure of sleep, Pittsburgh Sleep Quality Index (PSQI) [90] will be documented preoperatively. The PSQI measures characteristics of nighttime sleep in the prior month: producing a score of 0 – 21 (lower = better sleep) with a cut-off of $\geq$ 5 indicating poor sleep quality. Richards Campbell Sleep Questionnaire will be collected from the patient on POD 1 and POD 2 to document in-hospital quality of sleep. We will also collect the modified Fried Frailty Criteria at baseline.

c. Statistical plan including sample size justification and interim data analysis.

Choice of Sample Size; Power Considerations– Why 80 adherent participants? The power to detect a difference in the development of postoperative delirium of an the previously reported effect-size [24](30% placebo-treated vs. 3% ramelteon-treated) is greater than 0.90, using the current design of 40 participants in each treatment arm and assuming 30% of the placebo-treated group will develop delirium on POD 1 or 2. This design can detect an 80% reduction in delirium (30% placebo-treated vs. 6% ramelteon-treated) with a power of 0.84. A conservative estimate for power for the continuous outcome (DSRS-98R) measuring delirium severity can be derived by conceptualizing the proposed longitudinal analysis as an independent samples t-test. With alpha of 0.05 and a sample size of 80, and with means in the ramelteon and placebo groups of 5.75 and 11.34, respectively (as reported in Hatta, et al), and SDs of 4.16 and 10.96, we would have 84% power to detect that difference. Power for the planned analysis, which includes 3 post-surgery measurements per participant, and controls for baseline measurement and additional covariates would likely be greater.

Data Analysis-Specific Aim 1:
Analysis 1:Odds of postoperative delirium upon immediate recovery will be modeled via logistic regression with treatment assignment as the covariate of interest, and controlling for baseline MMSE, surgical duration and sleep disorders in all randomized participants in a strict intent to treat model and also in a second analysis among the 80 first-dose adherent participants.[91] Odds of delirium on POD's 1 and 2 will be modeled via a Markov logistic regression model [92] as a function of treatment assignment, baseline MMSE, and mental status on

the previous day, where two transitions are possible: from normal mental status to delirium and/or coma (abnormal mental states) and the reverse. Correlation of mental status on consecutive days for the same individual will be modeled using generalized estimating equations (GEE). [92] We will fit models with interactions between treatment group and variables hypothesized to predict treatment response, including baseline MMSE and sleep to determine if treatment response varies as a function of baseline predictors.

Analysis 2: The continuous DRS-98R severity measure of delirium will be modeled via longitudinal linear regression with correlated observations within participants addressed via the method of GEE with treatment assignment as the covariate of interest and controlling for baseline DRS-98R score, MMSE, surgical duration and sleep disorders.

Data Analysis-Specific Aim 2: Risk of a severe adverse event will be modeled as a function of treatment assignment using logistic regression, as will counts of total adverse events using ordinal logistic regression or Poisson regression as appropriate. Counts of each specific type of AE, as a function of treatment assignment will be scrutinized to determine the power needed to study them in future larger-scale trials.

d. Early stopping rules. This is a pilot study and will continue until 80 adherent participants are recruited. A Data Safety Monitoring Board will review the data at the end of year one or at recruitment of 40 adherent participants (whichever comes first) to review the unblinded (labelled "A" and "B") data for safety of the intervention. Specifically, for the analyses of rates of delirium in the two groups, we will use a Haybittle-Peto boundary such that the alpha for the interim analysis will be 0.001, and the alpha for the final efficacy analysis will be 0.05.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Risks associated with the Study Treatment: Ramelteon has FDA approval for use in elderly patients with insomnia. However this agent has never been used peri-operatively in older patients undergoing general or regional anesthesia and we cannot be certain that it will be safe in this setting. Therefore the study aims to test safety of this agent compared to placebo; we will systematically collect daily information on adverse (AE) and serious adverse events (SAE) that occur in each arm of the study. The main potential risk is one of increased incidence of delirium due to the treatment intervention. Other risks associated with the use of ramelteon reported in product labeling include: 1) angioedema and anaphylactic reactions – this risk is extremely rare; 2) worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities that may be the result of an unrecognized underlying psychiatric or physical disorder, such as worsening of depression (including suicidal ideation and completed suicides), hallucinations, bizarre behavior, agitation and mania; 4) amnesia, anxiety and other neuro-psychiatric symptoms may also occur unpredictably, including complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a hypnotic) and other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) with amnesia for the event; 5) decreased testosterone levels and increased prolactin levels have been reported with long-term use; 7) the use is contraindicated in severe hepatic failure as evidenced by cirrhosis, ascites, portal hypertension and prolonged bleeding times; 8) also contraindicated with the concomitant use of fluvoxamine; and finally 9) caution is to be used when prescribing with other CYP enzyme active agents such as rifampin, fluconazole, and ketoconazole. Other less serious side effects that have been reported in clinical trials include somnolence, fatigue, dizziness, nausea and worsened insomnia.

The following is taken from the ramelteon package insert:

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections:Severe anaphylactic and anaphylactoid reactions *[see Warnings and Precautions (5.1)]*Abnormal thinking, behavior changes, and complex behaviors *[see Warnings and Precautions (5.3)]* CNS effects *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Adverse Reactions Resulting in Discontinuation of Treatment

The data described in this section reflect exposure to ROZEREM in 5373 subjects, including 722 exposed for 6 months or longer, and 448 subjects for one year.

Six percent of the 5373 individual subjects exposed to ROZEREM in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 2279 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ROZEREM were somnolence, dizziness, nausea, fatigue, headache, and insomnia; all of which occurred in 1% of the patients or less.

ROZEREM Most Commonly Observed Adverse Events

Table 1 displays the incidence of adverse events reported by the 2861 patients with chronic insomnia who participated in placebo-controlled trials of ROZEREM.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Table 1. Incidence (% of subjects) of Treatment-Emergent Adverse Events

Term	Placebo (n= 1456)	Ramelteon 8 mg (n=1405)
Somnolence	2 %	3%
Fatigue	2%	3%
Dizziness	3%	4%
Nausea	2%	3%
Insomnia exacerbated	2%	3%

b. Steps taken to minimize the risks.

We will adhere to the exclusion criteria listed above which will help avoid the recruitment of patients most at risk of side effects and adverse consequences. Patients will be interviewed each day for any side effects and the medical records will be reviewed and the data collected for Aim 2 of the study. A DSMB will review the data as described above and the study will be halted if there is evidence of harm significantly associated with the intervention. We will also inform participants of the risks – particularly when taking the first dose at home. Specifically we will advise them to call 911 or come to an emergency room if, after taking the study drug, they develop any swelling, rash, difficulty or noisy breathing.

The clinical team (Attending Surgeon - eg., Co-Investigators: Khanuja, Sterling, Oni and the Chief of Anesthesiology - eg., Co-Investigator Sieber) will be notified by the study team should any patient be found to be delirious (thereby ineligible) during the screening process for the study. The Attending Surgeon (or his designee) will be responsible for contacting the patient's family and arranging subsequent follow-up of the patient - either in an emergency setting, in the clinic, or through early admission to hospital. The precise recommendation will be informed by the clinical status of the patient.

c. Plan for reporting unanticipated problems or study deviations.

All AE's and SAE's will be reported to the IRB and the DSMB in keeping with rules of the Johns Hopkins Institutional Review Board. As noted above – data on adverse effects will be collected each day of the study.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

As with any study incorporating research as a part of clinical care, there is a small but real risk of unintentional release of HPI. We will make every effort to secure data and study records under lock and key and encryption in keeping with institutional standards to prevent this from occurring.

e. Financial risks to the participants.

The financial risks to the participants related specifically to this protocol are minimal.

9. Benefits

a. Description of the probable benefits for the participant and for society.

While there may be no clear benefit for those participants who take part, this study is an important next step in the discovery of pharmaceutical agents in postoperative delirium prevention. **A positive outcome may help relieve suffering of many patients in our healthcare system in the future and stimulate further inquiry delineating the role of melatonin in the genesis of delirium, potentially benefiting society.**

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants whose participation requires an extra study visit prior to their surgery will be compensated $50. No payment is planned for those who are hospitalized prior to their surgery since all study activities will be conducted while they are inpatients. Study medication (including active agent – ramelteon or placebo) will be provided and administered free of charge to the patient.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.
The study budget will include payment for all of the additional procedures (i.e. urine on day of surgery, analysis of blood biomarkers at all time points) and drugs – both active and placebo, used in this study.

References

1. American Psychiatric Association, American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington, Va.: American Psychiatric Association; 2013.

2. Inouye SK. Delirium in older persons. *N Engl J Med.* 2006 Mar 16; 354(11): 1157-1165.

3. Jones RN, Fong TG, Metzger E, Tulebaev S, Yang FM, Alsop DC, Marcantonio ER, Cupples LA, Gottlieb G, Inouye SK. Aging, brain disease, and reserve: Implications for delirium. *Am J Geriatr Psychiatry.* 2010 Feb; 18(2): 117-127.

4. Fong TG, Jones RN, Marcantonio ER, Tommet D, Gross AL, Habtemariam D, Schmitt E, Yap L, Inouye SK. Adverse outcomes after hospitalization and delirium in persons with alzheimer disease. *Ann Intern Med.* 2012 Jun 19; 156(12): 848-56, W296. PMCID: PMC3556489.

5. Neufeld KJ, Leoutsakos JM, Sieber FE, Wanamaker BL, Gibson Chambers JJ, Rao V, Schretlen DJ, Needham DM. Outcomes of early delirium diagnosis after general anesthesia in the elderly. *Anesth Analg.* 2013 Aug; 117(2): 471-478. PMCID: PMC4017627.

6. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. *JAMA.* 2010 Jul 28; 304(4): 443-451.

7. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, Jones RN. Cognitive trajectories after postoperative delirium. *N Engl J Med.* 2012; 367: 30-39.

8. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW. Long-term cognitive impairment after critical illness. *N Engl J Med.* 2013 10/03; 2013/12; 369(14): 1306-1316.

9. Davis DH, Muniz Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE, Cunningham C, Polvikoski T, Sulkava R, MacLullich AM, Brayne C. Delirium is a strong risk factor for dementia in the oldest-old: A population-based cohort study. *Brain.* 2012 Sep; 135(Pt 9): 2809-2816. PMCID: PMC3437024.

10. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med.* 2008; 168: 27-32.

11. Leslie DL, Inouye SK. The importance of delirium: Economic and societal costs. *J Am Geriatr Soc.* 2011 Nov; 59 Suppl 2: S241-3.

12. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: Risk factors and outcomes. *Ann Surg.* 2009 Jan; 249(1): 173-178.

13. Fitzgerald JM, Adamis D, Trzepacz PT, O'Regan N, Timmons S, Dunne C, Meagher DJ. Delirium: A disturbance of circadian integrity? *Med Hypotheses.* 2013 Oct; 81(4): 568-576.

14. Mattoo SK, Grover S, Chakravarty K, Trzepacz PT, Meagher DJ, Gupta N. Symptom profile and etiology of delirium in a referral population in northern india: Factor analysis of the DRS-R98. *J Neuropsychiatry Clin Neurosci.* 2012 Winter; 24(1): 95-101.

15. Meagher DJ, Moran M, Raju B, Gibbons D, Donnelly S, Saunders J, Trzepacz PT. Motor symptoms in 100 patients with delirium versus control subjects: Comparison of subtyping methods. *Psychosomatics.* 2008 Jul-Aug; 49(4): 300-308.

16. Meagher DJ, Moran M, Raju B, Gibbons D, Donnelly S, Saunders J, Trzepacz PT. Phenomenology of delirium. assessment of 100 adult cases using standardised measures. *Br J Psychiatry.* 2007 Feb; 190: 135-141.

17. de Rooij SE, van Munster BC. Melatonin deficiency hypothesis in delirium: A synthesis of current evidence. *Rejuvenation Res.* 2013 Aug; 16(4): 273-278.

18. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: When cytokines and acetylcholine collide. *Lancet.* 2010 Feb 27; 375(9716): 773-775.

19. Field RH, Gossen A, Cunningham C. Prior pathology in the basal forebrain cholinergic system predisposes to inflammation-induced working memory deficits: Reconciling inflammatory and cholinergic hypotheses of delirium. *J Neurosci.* 2012 May 2; 32(18): 6288-6294. PMCID: PMC3359617.

20. Cunningham C, Maclullich AM. At the extreme end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behaviour response. *Brain Behav Immun.* 2013 Feb; 28: 1-13.

21. Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin--a pleiotropic, orchestrating regulator molecule. *Prog Neurobiol.* 2011 Mar; 93(3): 350-384.

22. Polimeni G, Esposito E, Bevelacqua V, Guarneri C, Cuzzocrea S. Role of melatonin supplementation in neurodegenerative disorders. *Front Biosci (Landmark Ed).* 2014 Jan 1; 19: 429-446.

23. Lin L, Huang QX, Yang SS, Chu J, Wang JZ, Tian Q. Melatonin in alzheimer's disease. *Int J Mol Sci.* 2013 Jul 12; 14(7): 14575-14593. PMCID: PMC3742260.

24. Hatta K, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C, Nakamura H, for the DELIRIA-J Group. Preventive effects of ramelteon on delirium: A randomized placebo-controlled trial. *JAMA Psychiatry.* 2014 Feb 19.

25. Neufeld KJ, Leoutsakos JS, Sieber FE, Joshi D, Wanamaker BL, Rios-Robles J, Needham DM. Evaluation of two delirium screening tools for detecting post-operative delirium in the elderly

. *Br J Anaesth.* 2013 May 8; 111(4): 612-618.

26. Sharma PT, Sieber FE, Zakriya KJ, Pauldine RW, Gerold KB, Hang J, Smith TH. Recovery room delirium predicts postoperative delirium after hip-fracture repair. *Anesth Analg.* 2005 Oct; 101(4): 1215-20, table of contents.

27. O'Regan NA, Fitzgerald J, Timmons S, O'Connell H, Meagher D. Delirium: A key challenge for perioperative care. *Int J Surg.* 2013; 11(2): 136-144.

28. Bruce AJ, Ritchie CW, Blizard R, Lai R, Raven P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. *Int Psychogeriatr.* 2007 Apr; 19(2): 197-214.

29. Young J, Inouye SK. Delirium in older people. *BMJ.* 2007 Apr 21; 334(7598): 842-846. PMCID: PMC1853193.

30. Sanders RD, Pandharipande PP, Davidson AJ, Ma D, Maze M. Anticipating and managing postoperative delirium and cognitive decline in adults. *BMJ.* 2011 Jul 20; 343: d4331.

31. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, Khuri SF, Lipsitz LA, Ramlawi B, Levitsky S, Marcantonio ER. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation.* 2009 Jan 20; 119(2): 229-236.

32. Rudolph JL, Jones RN, Rasmussen LS, Silverstein JH, Inouye SK, Marcantonio ER. Independent vascular and cognitive risk factors for postoperative delirium. *Am J Med.* 2007 Sep; 120(9): 807-813.

33. Rudolph JL, Inouye SK, Jones RN, Yang FM, Fong TG, Levkoff SE, Marcantonio ER. Delirium: An independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc.* 2010 Apr; 58(4): 643-649. PMCID: PMC2856754.

34. Trompeo AC, Vidi Y, Locane MD, Braghiroli A, Mascia L, Bosma K, Ranieri VM. Sleep disturbances in the critically ill patients: Role of delirium and sedative agents. *Minerva Anestesiol.* 2011 Jun; 77(6): 604-612.

35. Maldonado JR. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry.* 2013 Dec; 21(12): 1190-1222.

36. de Rooij SE, van Munster BC, de Jonghe A. Melatonin prophylaxis in delirium: Panacea or paradigm shift? *JAMA Psychiatry.* 2014 Feb 19.

37. Brzezinski A. Melatonin in humans. *N Engl J Med.* 1997 Jan 16; 336(3): 186-195.

38. Borjigin J, Li X, Snyder SH. The pineal gland and melatonin: Molecular and pharmacologic regulation. *Annu Rev Pharmacol Toxicol.* 1999; 39: 53-65.

39. Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. Melatonin and its analogs in insomnia and depression. *J Pineal Res.* 2012 May; 52(4): 365-375.

40. Pandi-Perumal SR, BaHammam AS, Brown GM, Spence DW, Bharti VK, Kaur C, Hardeland R, Cardinali DP. Melatonin antioxidative defense: Therapeutical implications for aging and neurodegenerative processes. *Neurotox Res.* 2013 Apr; 23(3): 267-300.

41. Lee EJ, Lee MY, Chen HY, Hsu YS, Wu TS, Chen ST, Chang GL. Melatonin attenuates gray and white matter damage in a mouse model of transient focal cerebral ischemia. *J Pineal Res.* 2005 Jan; 38(1): 42-52.

42. Lee EJ, Wu TS, Lee MY, Chen TY, Tsai YY, Chuang JI, Chang GL. Delayed treatment with melatonin enhances electrophysiological recovery following transient focal cerebral ischemia in rats. *J Pineal Res.* 2004 Jan; 36(1): 33-42.

43. Lee MY, Kuan YH, Chen HY, Chen TY, Chen ST, Huang CC, Yang IP, Hsu YS, Wu TS, Lee EJ. Intravenous administration of melatonin reduces the intracerebral cellular inflammatory response following transient focal cerebral ischemia in rats. *J Pineal Res.* 2007 Apr; 42(3): 297-309.

44. Rezzani R, Rodella LF, Bonomini F, Tengattini S, Bianchi R, Reiter RJ. Beneficial effects of melatonin in protecting against cyclosporine A-induced cardiotoxicity are receptor mediated. *J Pineal Res.* 2006 Oct; 41(3): 288-295.

45. Mathes AM, Kubulus D, Weiler J, Bentley A, Waibel L, Wolf B, Bauer I, Rensing H. Melatonin receptors mediate improvements of liver function but not of hepatic perfusion and integrity after hemorrhagic shock in rats. *Crit Care Med.* 2008 Jan; 36(1): 24-29.

46. Mathes AM, Kubulus D, Pradarutti S, Bentley A, Weiler J, Wolf B, Ziegeler S, Bauer I, Rensing H. Melatonin pretreatment improves liver function and hepatic perfusion after hemorrhagic shock. *Shock.* 2008 Jan; 29(1): 112-118.

47. Rathnasamy G, Ling EA, Kaur C. Therapeutic implications of melatonin in cerebral edema. *Histol Histopathol.* 2014 May 29.

48. Chen HY, Chen TY, Lee MY, Chen ST, Hsu YS, Kuo YL, Chang GL, Wu TS, Lee EJ. Melatonin decreases neurovascular oxidative/nitrosative damage and protects against early increases in the blood-brain barrier permeability after transient focal cerebral ischemia in mice. *J Pineal Res.* 2006 Sep; 41(2): 175-182.

49. Chen TY, Lee MY, Chen HY, Kuo YL, Lin SC, Wu TS, Lee EJ. Melatonin attenuates the postischemic increase in blood-brain barrier permeability and decreases hemorrhagic transformation of tissue-plasminogen activator therapy following ischemic stroke in mice. *J Pineal Res.* 2006 Apr; 40(3): 242-250.

50. Trzepacz PT. Update on the neuropathogenesis of delirium. *Dement Geriatr Cogn Disord.* 1999 Sep-Oct; 10(5): 330-334.

51. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. *J Psychosom Res.* 2008 Sep; 65(3): 229-238.

52. Cunningham C, Skelly DT. Non-steroidal anti-inflammatory drugs and cognitive function: Are prostaglandins at the heart of cognitive impairment in dementia and delirium? *J Neuroimmune Pharmacol.* 2012 Mar; 7(1): 60-73. PMCID: PMC3280386.

53. Maldonado JR. Pathoetiological model of delirium: A comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. *Crit Care Clin.* 2008 Oct; 24(4): 789-856, ix.

54. Cronin AJ, Keifer JC, Davies MF, King TS, Bixler EO. Melatonin secretion after surgery. *Lancet.* 2000 Oct 7; 356(9237): 1244-1245.

55. Shigeta H, Yasui A, Nimura Y, Machida N, Kageyama M, Miura M, Menjo M, Ikeda K. Postoperative delirium and melatonin levels in elderly patients. *Am J Surg.* 2001 Nov; 182(5): 449-454.

56. Yoshitaka S, Egi M, Morimatsu H, Kanazawa T, Toda Y, Morita K. Perioperative plasma melatonin concentration in postoperative critically ill patients: Its association with delirium. *J Crit Care.* 2013 Jun; 28(3): 236-242.

57. Sultan SS. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. *Saudi J Anaesth.* 2010 Sep; 4(3): 169-173. PMCID: PMC2980663.

58. de Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R, van Velde R, Levi M, de Haan RJ, de Rooij SE, de Rooij SE, on behalf of the Amsterdam Delirium Study Group. Effect of melatonin on incidence of delirium among patients with hip fracture: A multicentre, double-blind randomized controlled trial. *CMAJ.* 2014 Sep 2.

59. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M. Melatonin decreases delirium in elderly patients: A randomized, placebo-controlled trial. *Int J Geriatr Psychiatry.* 2011 Jul; 26(7): 687-694.

60. DailyMed current medication information website [homepage on the Internet]. . Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7a51d289-2013-4d37-adf2-91ea49df7932.

61. American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV : International version with ICD-10 codes. 4th , international version ed. Washington, DC: American Psychiatric Association; 1995.

62. Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the delirium rating scale-revised-98: Comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci.* 2001 Spring; 13(2): 229-242.

63. van Eijk MM, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, Slooter AJ. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: A multicentre, double-blind, placebo-controlled randomised trial. *Lancet.* 2010 Nov 27; 376(9755): 1829-1837.

64. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, Bernard GR, Dittus RS, Ely EW, for the MIND TI. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: The MIND randomized, placebo-controlled trial. *Crit Care Med.* 2010; 38: 428-437.

65. Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, Jackson J, Perkins GD, McAuley DF. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (hope-ICU): A randomised, double-blind, placebo-controlled trial. *Lancet Respir Med.* 2013 Sep; 1(7): 515-523.

66. Friedman JI, Soleimani L, McGonigle DP, Egol C, Silverstein JH. Pharmacological treatments of non-substance-withdrawal delirium: A systematic review of prospective trials. *Am J Psychiatry.* 2014 Feb 1; 171(2): 151-159.

67. Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS, Blow FC. Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry.* 2012 Jan; 169(1): 71-79.

68. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: Meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry.* 2006 Mar; 14(3): 191-210.

69. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. *JAMA.* 2005 Oct 19; 294(15): 1934-1943.

70. Zhdanova IV. Melatonin as a hypnotic: Pro. *Sleep Med Rev.* 2005 Feb; 9(1): 51-65.

71. Zammit G. Comparative tolerability of newer agents for insomnia. *Drug Saf.* 2009; 32(9): 735-748.

72. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005 Aug 4; 353(5): 487-497.

73. Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: A randomized trial. *Anesthesiology.* 2012; 116: 987-997.

74. Silverstein JH, Deiner SG. Perioperative delirium and its relationship to dementia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012; 43C: 108-115.

75. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975 Nov; 12(3): 189-198.

76. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horowitz RI. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* 1990; 113(12): 941-948.

77. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA.* 2016 Feb 23; 315(8): 801-810.

78. Roth T, Seiden D, Wang-Weigand S, Zhang J. A 2-night, 3-period, crossover study of ramelteon's efficacy and safety in older adults with chronic insomnia. *Curr Med Res Opin.* 2007 May; 23(5): 1005-1014.

79. Wurtman R. Ramelteon: A novel treatment for the treatment of insomnia. *Expert Rev Neurother.* 2006 Jul; 6(7): 957-964.

80. Wechsler D, editor. Wechsler adult intelligence scale. Third ed. San Antonio: The Psychological Corporation Harcourt Brace & Company; 1997.

81. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* 1990 Dec 15; 113(12): 941-948.

82. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA.* 2001 Dec 5; 286(21): 2703-2710.

83. Jorm AF. The informant questionnaire on cognitive decline in the elderly (IQCODE): A review. *Int Psychogeriatr.* 2004 Sep; 16(3): 275-293.

84. Morris JC. The clinical dementia rating (CDR): Current version and scoring rules. *Neurology.* 1993 Nov; 43(11): 2412-2414.

85. KATZ S, FORD AB, MOSKOWITZ RW, JACKSON BA, JAFFE MW. Studies of illness in the aged. the index of adl: A standardized measure of biological and psychosocial function. *JAMA.* 1963 Sep 21; 185: 914-919.

86. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist.* 1970 Spring; 10(1): 20-30.

87. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969 Autumn; 9(3): 179-186.

88. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis.* 1987; 40(5): 373-383.

89. ASA physical status classification system [homepage on the Internet]. . Available from: http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.

90. Buysse DJ, Reynolds CF,3rd, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res.* 1989 May; 28(2): 193-213.

91. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: Current practice and problems. *Stat Med.* 2002 Oct 15; 21(19): 2917-2930.

92. Diggle PJ, Liang KY, and Zeger SL. Analysis of longitudinal data. Oxford: Clarendon Press; 1994