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ORIGINAL ARTICLE

Results from a double blinded, randomised, placebo-controlled, feasibility trial of melatonin for the treatment of delirium in older medical inpatients

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Key words

delirium, melatonin, treatment, sleep, neurocognitive disorder, sepsis-associated encephalopathy.

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Abstract

Background: Delirium is common in elderly inpatients, causing distress, cognitive decline and death. No known intervention improves the course of delirium; current treatments are symptomatic, and limited by lack of efficacy and adverse effects. There is an urgent need to find an effective treatment for delirium.

Aims: To determine the feasibility of a trial of oral melatonin 5 mg nightly for five nights for the treatment of delirium in older medical inpatients, and determine the participants required to demonstrate a clinically and statistically significant decrease in severity of delirium in older medical inpatients treated with melatonin.

Methods: This was a double blinded, randomised controlled trial in general internal medicine units of a tertiary teaching hospital. Older (≥ 70 years) inpatients with confusion assessment method positive hyperactive or mixed delirium were suitable for inclusion. Subjects received melatonin 5 mg oral nightly for five nights or matching placebo. The primary outcome was the Memorial Delirium Assessment Scale (MDAS) administered daily.

Results: No adverse effects occurred due to melatonin. In the treatment group, the mean change in MDAS from baseline during treatment period was 2.5 ± 5.0 points, in the placebo group, 2.1 ± 4.1 points, a non-significant difference. A power calculation accounting for drop-out (31.0%), suggests 120 participants would be required to demonstrate with 90% power that melatonin 5 mg reduces the severity of delirium by 3 points or more on MDAS.

Conclusions: A trial of the hypothesis that 5 mg melatonin nightly for five nights reduces delirium severity in older medical inpatients would require 120 patients, and is feasible.

Introduction

Delirium is a common condition affecting up to one fifth of hospitalised older adults^{1,2} and often undiagnosed.³ It is associated with poor outcomes, including long-term cognitive decline,⁴ functional decline,⁵ institutionalisation⁶ and mortality.⁷ Delirium is a syndrome with an acute, fluctuating course with disturbance of attention, awareness, psychomotor state and perception.⁸ Pharmacological

treatments shown to be a mildly effective symptomatic treatment include antipsychotics, although they are associated with adverse effects.^{9,10} Other agents are not recommended due to lack of evidence of efficacy and, or adverse effects.¹¹ Disturbance of sleep and circadian rhythm is common in delirium, where sleep–wake cycle reversal, hypersomnolence, and hyperactivity are all recognised phenomena,¹² and a potential mechanism links delirium and sleep.¹³

Melatonin (*N*-acetyl-5-methoxytryptamine) is a hormone and neurotransmitter derived from the pineal gland that regulates circadian rhythm. Abnormalities of melatonin physiology have been demonstrated in delirium. Low levels of urinary metabolites have been found in hyperactive delirious patients, whereas high levels

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were associated with hypoactive motor states,^{14–16} suggesting a melatonin deficiency in hyperactive but not hypoactive delirium. Abnormalities of tryptophan (from which melatonin is derived) metabolism including low metabolites suggestive of low melatonin secretion are associated with post-operative and critical care delirium.^{17,18} Case reports of successful treatment of delirium with melatonin have been published,¹⁴ but no randomised controlled trials of melatonin for the treatment of delirium. Some indications of the efficacy of melatonin for the treatment of delirium can be derived from studies of incident delirium where melatonin was continued if delirium occurred. In a trial of 0.5 mg in medical inpatients melatonin decreased delirium incidence but had no effect on delirium severity when it developed.¹⁹ Sultan *et al.* conducted a trial of 5 mg melatonin versus no treatment, clonidine or midazolam pre-operatively for hip arthroplasty also reported reduced delirium incidence.²⁰ Melatonin was continued for three nights if delirium developed; this was reported to be effective for treatment of delirium that occurred but no validated scale or control was used.²⁰ In contrast, a trial of 3 mg in fractured neck of femur patients showed no effect on delirium incidence or severity.²¹ Thus, the evidence for melatonin for as effective and the appropriate dose for the treatment of delirium is unclear. Melatonin currently cannot be recommended for the treatment of delirium on the basis of current evidence.

We aimed to determine the feasibility of, and number of participants required in, a study that would determine if 5 mg melatonin nightly for five nights reduces the severity of delirium in medical inpatients with delirium.

Methods

Trial design

The protocol of this trial has previously been published elsewhere.²² This was a single-centre, randomised, placebo-controlled trial of 5 mg melatonin or placebo for five nights with an additional two nights of follow-up between May 2014 and June 2016. The study was conducted after approval by the Human Research Ethics Committee at the Royal Melbourne Hospital, Australia, and was conducted in concordance with Good Clinical Practice guidelines. Patients with delirium are generally considered to lack the capacity to consent. As such, written informed consent was provided by a surrogate decision maker who could provide legal consent that would hold until the patient's capacity to consent returned. The trial is registered with the Australia New Zealand Clinical Trials Registry (trial ID: ACTRN12614000101684). There were no changes to the trial or protocol once it had

started. The trial and reporting conforms to CONSORT guidelines.

Participants and setting

The study was conducted at The Royal Melbourne Hospital, Parkville, Australia, a 550-bed acute teaching hospital. The study population consisted of general medical inpatients aged 70 years or older. Potential participants were identified by discussion of new admissions to the units at handover meetings and referral by medical staff of units following information and advertisement of the trial. Patients were screened for delirium by trained, medically qualified research team members using the confusion assessment method (CAM),²³ a well described and validated tool for this purpose, with reference to the notes and discussion with treating team nursing, allied health and medical staff where the diagnosis was not clear. Participants could be included if delirium was diagnosed. Patients were excluded if they were unable to understand or communicate in English, had taken melatonin or a melatonin receptor agonist within the preceding 14 days, were unlikely to complete the trial – defined as an expected prognosis or planned further admission to hospital of less than 7 days, had a contraindication to melatonin (severe hepatic failure, an active seizure disorder or concomitant cimetidine use) or had an exclusively hypoactive delirium.

Randomisation and blinding

After applying inclusion and exclusion criteria, patients were randomly allocated to treatment (5 mg melatonin) or control (placebo) in a 1:1 ratio. Before the start of the study an independent statistician generated randomised allocation codes within permuted blocks of four patients (two placebo and two treatment). The results were unknown to any investigators, care-givers or administration staff. A separate code sheet was kept locked in the trial pharmacy to allow matching after completion of the trial and in the event of an adverse event where that might be necessary.

Procedures

Patients received the study medication for five consecutive nights at 8 pm. The study preparation contained either melatonin 5 mg or placebo in identically packaged high-density polyethylene containers of five capsules each.

Baseline data including age, sex, delirium severity, smoking status, alcohol consumption, dementia status through Informant Questionnaire on COgnitive Decline in the Elderly, short form (IQCODE)²⁴ and chart review, comorbidities (Charlson Comorbidity Index²⁵),

psychiatric history including depressive symptoms, premorbid function (Barthel index of activities of daily living), medications and potential delirium precipitants – classified as infectious/inflammatory, pain, metabolic – were recorded. Electrolytes and liver function tests were recorded for the same purpose. The motor subtype of delirium was assessed by the clinical judgement of the investigators due to the lack of a validated tool at the start of the trial.

Following enrolment, patients were visited daily by trained research staff for 7 days (5 days of medication and 2 after completion) to collect primary and secondary outcome and assess safety. Adverse events were reported to an independent safety monitor for assessment for severity and relationship to the intervention.

Objectives, outcomes and delirium assessment

The first objective was to determine the feasibility of a trial of oral Melatonin 5 mg nightly for five nights for

Table 1 Schedule of procedures

Procedure	Baseline (D0)	Treatment (D1-5)	Post-treatment (D6-7)
Consent	X		
Age	X		
Sex	X		
Electrolytes	X		
Liver function	X		
MMSE	X	X	X
Digit Span Forwards and Backwards	X	X	X
CAM	X	X	X
MDAS	X	X	X
Motor subtype	X		
IQCODE	X†		
CCI	X†		
Barthel index	X		
Presence of restraints		X	X
Number of falls		X	X
Number of pressure areas	X‡	X	X
Rescue medication		X	X
Adverse events		X	X
Review INR	X§	X§	

†The IQCODE and CCI was measured at entry if possible but could be measured at any point during the trial. ‡Initial number and location of pressure areas was recorded at entry in order to derive the number of new areas at each subsequent visit. §If participant was on warfarin, the INR was performed every 1–2 days as per standard practice of the treating team for acutely unwell inpatients when warfarinised. CAM, confusion assessment method; CCI, Charlson Comorbidity Scale; D(#), day number; INR, International Normalised Ratio; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MDAS, Memorial Delirium Assessment Scale; MMSE, mini-mental state examination.

the treatment of delirium in older medical inpatients. The second objective was to determine the number of participants required to demonstrate a clinically and statistically significant decrease in the primary trial outcome.

The primary trial outcome was delirium severity assessed using the Memorial Delirium Assessment Scale (MDAS).²⁶ This was calculated from change in MDAS scores from baseline to the average over Days 1–5 as a marker of symptom severity. We had *a priori* defined a clinically significant difference as 3 points improvement on the MDAS, by comparison to the sole placebo controlled trial of an antipsychotic (quetiapine, an accepted treatment for delirium) for delirium demonstrating a change of similar extent.²⁷ MDAS is a validated scale, scored from 0 to 30, positively correlated with severity with good internal consistency and inter-rater reliability,

Table 2 Baseline characteristics of the study participants

Characteristic	Melatonin, n = 14	Placebo, n = 14
Age, mean ± SD (years)	85.1 ± 6.5	86.1 ± 4.4
Female sex, n (%)	8 (61.5)	7 (46.7)
MDAS Day 0, mean ± SD	14.4 ± 6.7	16.7 ± 4.6
Current smoker, n (%)	0	1 (6.7)
Ex smoker, n (%)	4 (30.8)	2 (13.3)
Never smoked, n (%)	9 (69.2)	9 (60.0)
Alcohol use, n (%)		
Excessive (>3 units/day)	0	0
Moderate (3–0 units/day)	4 (30.8)	3 (20.0)
None	9 (69.2)	9 (60.0)
Dementia, n (%)		
History of dementia	6 (46.2)	8 (53.3)
IQCODE ≥3.45	6 (46.2)	10 (66.7)
IQCODE ≥3.45 and/or history	10 (76.9)	11 (73.3)
MMSE, mean ± SD	8.7 ± 5.7	12.6 ± 8.8
History of delirium	0 (0)	2 (13.3)
Depression		
History of depression, n (%)	4 (30.8)	0 (0)
CCI, mean ± SD	6.1 ± 1.8	6.2 ± 1.3
Barthel index, mean ± SD	16.2 ± 5.5	14.9 ± 5.2
Medications, n (%)		
Anticholinergics	2 (15.4)	0 (0)
Opioids	4 (30.7)	2 (13.3)
Antipsychotics	1 (7.7)	2 (13.3)
Precipitating factors‡, n (%)		
Inflammation or sepsis	8 (61.5)	6 (40.0)
Injury or pain	5 (38.5)	5 (33.3)
Metabolic	1 (7.7)	3 (20.0)
Cardiovascular	2 (15.3)	1 (6.7)

†Continuous variables assessed using Student's t-test, categorical Fisher's exact test (two sided). ‡Some patients had more than one precipitating factor. CCI, Charlson Comorbidity Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MDAS, Memorial Delirium Assessment Scale; MMSE, mini-mental state.

Figure 1 Consort flow diagram.

that is derived from scores on the Folstein Mini-Mental State Examination,²⁸ and Digit Span Forwards and Digit Span Backwards.²⁶

Secondary trial outcomes included the change in mean MDAS scores over Days 1–5 (treatment period) to the mean on Days 6–7, and delirium duration (number of days CAM positive). Delirium presence or absence was assessed daily by the CAM. Other secondary

outcomes were: a reduction in other delirium management methods as measured by number of uses of restraints and number and dose of rescue medications, specifically benzodiazepines and antipsychotics, each day, and sleep quality as assessed with item 10 of the MDAS.

Safety outcomes were assessed by recording number of falls and pressure areas occurring or developing during active treatment (Table 1).

Table 3 Results

Outcome	Melatonin (n = 14)	Placebo (n = 14)	P- value†
Primary			
Change in MDAS baseline to treatment	2.54 ± 5.02	2.16 ± 4.13	0.413
Secondary			
Change in MDAS treatment to post-treatment	0.41 ± 3.21	1.42 ± 2.90	0.196
Number of days CAM+, median (IQR)	4.5 (3–5)	5 (5–5)	0.178
Number of falls Days 1–5	2	0	0.485
Number of new pressure areas Days 1–5	0	0	1.000
Use of rescue medications Days 1–5	10	13	0.780
MDAS item 10 (sleep) Days 1–5, mean ± SD	1.23 ± 0.23	1.63 ± 0.70	0.094
Use of restraints Days 1–5	0	0	1.000

†Continuous, normally distributed variables assessed using Student's *t*-test, non-normally distributed Wilcoxon rank-sum test, categorical Fisher's exact test (two sided). CAM, confusion assessment method; IQR, interquartile range; MDAS, Memorial Delirium Assessment Scale.

Power calculation

As one of the feasibility objectives was to obtain the standard deviation of the primary outcome measure to allow a power calculation and the subsequent development of an appropriately powered trial, a true power calculation was unable to be performed.

Statistical analysis

Data were collected daily for 7 days. The primary and secondary outcome measures were compared using a Student's *t*-test for normally distributed data or Mann–Whitney test for non-normally distributed continuous variables. Control and treatment group homogeneity was tested with Chi-squared statistics. For discrete outcomes, results were tested using a Chi-squared test. Where expected cell counts were less than seven Fisher's exact test (two sided) substituted for Chi-squared test, with the addition method used where cell counts were zero. The missing data were handled for the analysis using the last

observation carried forward method as per protocol. A *P*-value of less than 0.05 was considered significant.

Results

One hundred and fifty-four potential participants were assessed for eligibility. Eighty patients did not meet inclusion or met exclusion criteria. Forty-five surrogate decision-makers did not provide consent to participation, with 29 potential inpatients randomised.

Table 2 shows the baseline characteristics of the inpatients. The melatonin and placebo groups were well balanced. Alcohol consumption was low in all groups suggesting against alcohol withdrawal as a possible cause of the presentation with delirium.

Figure 1 illustrates the flow of participants through the trial. One participant in the placebo group succumbed to a haemorrhagic stroke prior to receiving any intervention but after enrolment so was excluded from the analysis. Five patients deceased during the trial, one in the melatonin group, four in the placebo group. None was assessed as related to the intervention. Four patients were transferred out of the study site or discharged from hospital prior to completion of trial procedures, three in the melatonin group and one in the placebo group, for 9 out of 30 (31.0%) unable to complete in total. This resulted in 11.0% of observations unavailable, a further 0.9% of observations were missing due to inability to perform outcome measures during the trial – most often when participants were not available due to attending an investigation or procedure. Overall 11.9% of observations were unavailable, these were dealt with using the last observation carried forward method. No participants or their surrogate decision maker declined to participate further once enrolled. The trial finished due to adequate recruitment.

Baseline MDAS was lower in the melatonin group (14.4 ± 6.7 vs 16.7 ± 4.6) suggesting lower delirium severity, though not significantly ($P = 0.247$). The primary outcome, improvement in MDAS from baseline to mean over Days 1–5, was not statistically significantly different between the two groups (treatment 2.5 ± 5.0 vs placebo 2.2 ± 4.1 , $P = 0.413$) 95% confidence intervals $(-7.5, 10)$ and $(-6, 10.4)$. There was a trend to significance in the mean MDAS item 10 (sleep disturbance subscale, from 0 to 4) towards lower scores in the melatonin group (1.2 ± 0.2 vs 1.6 ± 0.7 , $P = 0.094$). None of the safety-related outcomes was significantly different. No adverse events related to melatonin use occurred. Further results are displayed in Table 3.

Given the placebo group mean improvement in MDAS of 2.1 ± 4.1 , and using a two sided calculation with an alpha level of 0.05 and beta 0.9, two groups of

41 inpatients would be required to demonstrate a statistically significant difference of 3 points on the MDAS scale. Accounting for drop-out, 60 participants in each group for a total number of 120 inpatients would be required to demonstrate with 90% power that melatonin 5 mg reduces the severity of delirium over 5 days of treatment by 3 points or more on MDAS.

Discussion

In this feasibility trial we demonstrated that treatment with melatonin 5 mg for delirium in hospitalised older medical inpatients is feasible. Improvement in MDAS from baseline to mean over Days 1–5 was not statistically significant between treatment and placebo groups. A trend to less sleep disturbance was noted in the melatonin group. The 95% confidence interval of the primary outcome in the intervention group was $(-7.5, 10)$ and placebo $(-6, 10.4)$, thus a range of possible hypotheses are consistent with these results including: no effect of melatonin, and superiority of melatonin over placebo at the *a priori* level of 3 or more points. A definitive trial to differentiate these hypotheses would require a total of 120 participants.

There is a strong need to develop effective treatment for delirium as prevention cannot totally prevent the incidence of delirium.²⁹ Delirium in hospitalised patients can be prevented through non-pharmacological means;^{29,30} however, these methods have been trialled in established delirium and found not to decrease severity or reduce duration in comparison to usual care.³¹ Delirium has a high prevalence at admission to hospital,¹ therewith not all may be prevented. Therefore, there are several patients with delirium that would benefit from effective treatment. Delirium is a dangerous and distressing condition; there is an urgent need to find agents and methods that can effectively and safely treat delirium.³²

Several treatments have been previously evaluated: antipsychotics, melatonin and its agonists, and acetylcholinesterase inhibitors. Antipsychotics have been trialled for the management of symptoms of delirium, but are not recommended in all cases of delirium.³³ Quetiapine has been compared to placebo for the treatment of delirium in general hospital inpatients with the treated group improving faster but no significant improvement on severity scores.²⁷ Compared to placebo, risperidone and haloperidol produced significantly worse severity scores in palliative care patients with delirium.³⁴ Other trials have been between antipsychotics or usual care using benzodiazepines. In meta-analyses, antipsychotics have been reported as either ineffective for treatment³⁵ or when divided into first (haloperidol) and

second generation antipsychotics, second generation antipsychotics have been reported as decreasing severity and duration of delirium compared to haloperidol.³⁶ Thus antipsychotics have been the most studied agent, and may have a role in the treatment of delirium but this is uncertain, they may be deleterious.

Given the important role of acetylcholine in delirium and the deleterious role of anticholinergic drugs, several uncontrolled trials and case reports suggested rivastigmine^{37–41} and other acetylcholinesterase inhibitors^{42–46} might be useful for delirium treatment or prevention. However, a randomised double blinded controlled trial of prophylactic rivastigmine oral solution in cardiac surgery patients for delirium was negative.⁴⁷ rivastigmine oral solution underwent evaluation in a double blinded randomised controlled trial in delirium in intensive care unit (ICU) for the treatment of delirium with the hypothesis to increasing acetylcholine would reduce the duration, but the trial was stopped early due to an excess of deaths in the treatment arm,⁴⁸ substantially reducing interest of trials of this type, including a trial under development by an author of this paper (ACTRN12609001020279). Recently, a published trial of rivastigmine topical patch for the prevention and treatment of delirium in older patients with cognitive impairment requiring hip fracture surgery demonstrated some promising results with severity and incidence both reduced, but the authors recommend further study⁴⁹ and the result and safety should be confirmed in light of previous results.

Melatonin holds promise as a safe medication with few disease or medication interactions⁵⁰ that may effectively treat delirium in acutely unwell patients with multi-morbidities. Case reports and series report treatment efficacy, but this has not been evaluated in trials designed for the evaluation of treatment of delirium to reduce severity. Melatonin has been trialled for prophylaxis in doses of 0.5, 3 and 5 mg, and in those trials melatonin was continued if delirium developed, giving some indication regarding the ability of melatonin to reduce the severity of delirium.^{19–21,51} In the 0.5 and 3 mg trials no significant effect was demonstrated, and in the 5 mg trial a validated scale of delirium severity was not used. However, it may be that where melatonin treatment has failed to prevent delirium it may also fail to decrease severity. Current evidence does not support a role for melatonin in the treatment of delirium severity though this has not been appropriately evaluated. Ramelteon is a melatonin receptor agonist with substantially more potency at the melatonin receptor (estimated at 6–8 times as potent)⁵² that has a longer half-life than melatonin.^{53,54} Ramelteon has published case reports, series

and observational studies as a prophylactic^{55,56} and treatment^{57,58} agent against delirium with some suggested efficacy. Prophylaxis has been evaluated in placebo controlled trial in elderly medical and ICU inpatients where staff assessing outcomes and patients (but not treating staff) were blinded to the treatment status and found to significantly prevent delirium.⁵⁹ A trial in ICU patients of 8 mg ramelteon daily showed decreased duration and incidence of delirium though the primary outcome of stay in ICU had only a statistical trend to improvement.⁶⁰ Ramelteon has not been subject to a randomised controlled trial for the treatment of delirium.

Strength and limitations

Strengths of this trial include the pragmatic design with few exclusions of patients for medical reasons. Delirium is a condition with many causes and overwhelmingly affects patients with comorbidities, this has affected enrolment in trials of medications with more potential adverse effects resulting in slow recruitment.⁶¹ Lack of surrogate consent was the reason for the low enrolment of suitable inpatients. However, this rate of refusal is consistent with other intervention trials for patients with delirium.⁶² There is no evidence to suggest a systemic bias as a result of this that might affect the generalisability of results. A limitation of this study was the high rate of drop-out. In this context of a pilot trial this assists planning for a definitive trial and highlights the importance of finding an effective treatment for this highly morbid condition.

Conclusion

In summary, antipsychotics have the most evidence for the treatment of delirium but are not effective in all cases and may be deleterious; acetylcholinesterase inhibitors, melatonin and ramelteon are at this time not recommended for the treatment of delirium on the basis of current evidence. A definitive trial of 5 mg melatonin nightly for five nights for the treatment of delirium in hospitalised elderly would add to the body of knowledge regarding the treatment of delirium.

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References

- 1 Travers C, Byrne G, Pachana N, Klein K, Gray L. Prospective observational study of dementia and delirium in the acute hospital setting. *Intern Med J* 2013; **43**: 262–9.
- 2 Bellelli G, Morandi A, Di Santo SG, Mazzone A, Cherubini A, Mossello E *et al.* "Delirium Day": a nationwide point prevalence study of delirium in older hospitalized patients using an easy standardized diagnostic tool. *BMC Med* 2016; **14**: 106.
- 3 Lange PW, Lamanna M, Watson R, Maier AB. Undiagnosed delirium is frequent and difficult to predict: results from a prevalence survey of a tertiary hospital. *J Clin Nurs* 2019; **28**: 2537–42.
- 4 Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol* 2009; **5**: 210–20.
- 5 Vochteloo AJ, Moerman S, Tuinebreijer WE, Maier AB, de Vries MR, Bloem RM *et al.* More than half of hip fracture patients do not regain mobility in the first postoperative year. *Geriatr Gerontol Int* 2013; **13**: 334–41.
- 6 Krogseth M, Wyller TB, Engedal K, Juliebø V. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. *J Psychosom Res* 2014; **76**: 68–74.
- 7 Kiely DK, Marcantonio ER, Inouye SK, Shaffer ML, Bergmann MA, Yang FM *et al.* Persistent delirium predicts greater mortality. *J Am Geriatr Soc* 2009; **57**: 55–61.
- 8 Deffner T, Schönle J, Neyer FJ, Schulze J. Assessment of mental symptoms in intensive care unit patients: suggestion for a German version of the intensive care psychological assessment tool. *Med Klin Intensivmed Notfmed* 2019; **5**: 5.
- 9 Thom RP, Mock CK, Teslyar P. Delirium in hospitalized patients: risks and benefits of antipsychotics. *Cleve Clin J Med* 2017; **84**: 616–22.
- 10 Schrijver EJ, de Graaf K, de Vries OJ, Maier AB, Nanayakkara PW. Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: a systematic review of current evidence. *Eur J Intern Med* 2016; **27**: 14–23.
- 11 Loneragan E, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. *Cochrane Database Syst Rev* 2009; CD006379.
- 12 Fitzgerald JM, O'Regan N, Adamis D, Timmons S, Dunne CP, Trzepacz PT *et al.* Sleep-wake cycle disturbances in elderly acute general medical inpatients: longitudinal relationship to delirium and dementia. *Alzheimers Dement (Amst)* 2017; **7**: 61–8.
- 13 Kyeong S, Choi SH, Eun Shin J, Lee WS, Yang KH, Chung TS *et al.* Functional connectivity of the circadian clock and neural substrates of sleep-wake disturbance in delirium. *Psychiatry Res* 2017; **264**: 10–12.
- 14 Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. *Anesth Analg* 2002; **94**: 338–9.
- 15 Angeles-Castellanos M, Ramírez-Gonzalez F, Ubaldo-Reyes L, Rodríguez-Mayoral O, Escobar C. Loss of melatonin daily rhythmicity is associated with delirium development in hospitalized older adults. *Sleep Sci* 2016; **9**: 285–8.
- 16 Balan S, Leibovitz A, Zila SO, Ruth M, Chana W, Yassica B *et al.* The relation between the clinical subtypes of delirium and the urinary level of 6-SMT. *J Neuropsychiatry Clin Neurosci* 2003; **15**: 363–6.
- 17 Robinson TN, Raeburn CD, Angles EM, Moss M. Low tryptophan levels are associated with postoperative delirium in the elderly. *Am J Surg* 2008; **196**: 670–4.
- 18 van der Mast RC, Fekkes D, Moleman P, Peppinkhuizen L. Is postoperative delirium related to reduced plasma tryptophan? *Lancet* 1991; **338**: 851–2.
- 19 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; **26**: 687–94.
- 20 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; **4**: 169–73.
- 21 de Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R *et al.* Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. *CMAJ* 2014; **186**: E547–56.
- 22 Clayton-Chubb DI, Lange PW. Moderate dose melatonin for the abatement and treatment of delirium in elderly general medical inpatients: study protocol of a placebo controlled, randomised, double blind trial. *BMC Geriatr* 2016; **16**: 54.
- 23 Inouye SK, van Dyck C, 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; **113**: 941–8.
- 24 Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. *Psychol Med* 1994; **24**: 145–53.
- 25 Maes M, Vandoolaeghe E, Degroote J, Altamura C, Roels C, Hermans P. Linear CT-scan measurements in alcohol-dependent patients with and without delirium tremens. *Alcohol* 2000; **20**: 117–23.
- 26 Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *J Pain Symptom Manage* 1997; **13**: 128–37.
- 27 Tahir TA, Eeles E, Karapareddy V, Muthuvelu P, Chapple S, Phillips B *et al.* A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. *J Psychosom Res* 2010; **69**: 485–90.
- 28 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; **12**: 189–98.
- 29 Hsieh TT, Yue J, Oh E, Puella M, Dowal S, Trivison T *et al.* Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med* 2015; **175**: 512–20.
- 30 Kang J, Lee M, Ko H, Kim S, Yun S, Jeong Y *et al.* Effect of nonpharmacological interventions for the prevention of delirium in the intensive care unit: a systematic review and meta-analysis. *J Crit Care* 2018; **48**: 372–84.
- 31 Marcantonio ER, Bergmann MA, Kiely DK, Orav EJ, Jones RN. Randomized trial of a delirium abatement program for postacute skilled nursing facilities. *J Am Geriatr Soc* 2010; **58**: 1019–26.

- 32 Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. *JAMA* 2017; **318**: 1161–74.
- 33 National Institute for Health and Care Excellence (NICE). *Delirium in adults*. Quality standard [QS63]. London: NICE; 2014 [cited 2021 Jan 14]. Available from URL: <https://www.nice.org.uk/guidance/qs63/>
- 34 Agar MR, Lawlor PG, Quinn S, Draper B, Caplan GA, Rowett D *et al*. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. *JAMA Intern Med* 2017; **177**: 34–42.
- 35 Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2016; **64**: 705–14.
- 36 Kishi T, Hirota T, Matsunaga S, Iwata N. Antipsychotic medications for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. *J Neurol Neurosurg Psychiatry* 2016; **87**: 767–74.
- 37 Dautzenberg PL, Mulder LJ, Olde Rikkert MG, Wouters CJ, Loonen AJ. Adding rivastigmine to antipsychotics in the treatment of a chronic delirium. *Age Ageing* 2004; **33**: 516–7.
- 38 Kalisvaart CJ, Boelaarts L, de Jonghe JF, Hovinga IM, Kat MG. Successful treatment of three elderly patients suffering from prolonged delirium using the cholinesterase inhibitor rivastigmine. *Ned Tijdschr Geneesk* 2004; **148**: 1501–4.
- 39 Oldenbeuving AW, de Kort PLM, Jansen BPW, Kappelle LJ, Roks G. A pilot study of rivastigmine in the treatment of delirium after stroke: a safe alternative. *BMC Neurol* 2008; **8**: 34.
- 40 Scicutella A. Rivastigmine treatment of Othello syndrome and post-ECT delirium in a patient with Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2015; **27**: e90.
- 41 van den Blik BM, Maas HA. Successful treatment of three elderly patients suffering from prolonged delirium using the cholinesterase inhibitor rivastigmine. *Ned Tijdschr Geneesk* 2004; **148**: 2149; author reply 2149.
- 42 Marcantonio ER, Palihniach K, Appleton P, Davis RB. Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture. *J Am Geriatr Soc* 2011; **59**(Suppl 2): S282–8.
- 43 Sampson EL, Raven PR, Ndhlovu PN, Vallance A, Garlick N, Watts J *et al*. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry* 2007; **22**: 343–9.
- 44 Liptzin B, Laki A, Garb JL, Fingerroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry* 2005; **13**: 1100–6.
- 45 Wengel SP, Burke WJ, Roccaforte WH. Donepezil for postoperative delirium associated with Alzheimer's disease. *J Am Geriatr Soc* 1999; **47**: 379–80.
- 46 Wengel SP, Roccaforte WH, Burke WJ. Donepezil improves symptoms of delirium in dementia: implications for future research. *J Geriatr Psychiatry Neurol* 1998; **11**: 159–61.
- 47 Gamberini M, Bolliger D, Lurati Buse GA, Burkhardt CS, Grapow M, Gagneux A *et al*. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery – a randomized controlled trial. *Crit Care Med* 2009; **37**: 1762–8.
- 48 van Eijk MM, Roes KCB, Honing MLH, Kuiper MA, Karakus A, van der Jagt M *et al*. 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; **376**: 1829–37.
- 49 Youn YC, Shin HW, Choi BS, Kim SY, Lee JY, Ha YC. Rivastigmine patch reduces the incidence of postoperative delirium in older patients with cognitive impairment. *Int J Geriatr Psychiatry* 2017; **32**: 1079–84.
- 50 de Rooij SE, van Munster BC. Melatonin deficiency hypothesis in delirium: a synthesis of current evidence. *Rejuvenation Res* 2013; **16**: 273–8.
- 51 Jaiswal SJ, McCarthy TJ, Wineinger NE, Kang DY, Song J, Garcia S *et al*. Melatonin and sleep in preventing hospitalized delirium: a randomized clinical trial. *Am J Med* 2018; **131**: 1110–1117.e4.
- 52 Ramelteon: TAK 375. *Drugs R D* 2005; **6**: 186–8.
- 53 Karim A, Tolbert D, Cao C. Disposition kinetics and tolerance of escalating single doses of ramelteon, a high-affinity MT1 and MT2 melatonin receptor agonist indicated for treatment of insomnia. *J Clin Pharmacol* 2006; **46**: 140–8.
- 54 Greenblatt DJ, Harmatz JS, Karim A. Age and gender effects on the pharmacokinetics and pharmacodynamics of ramelteon, a hypnotic agent acting via melatonin receptors MT1 and MT2. *J Clin Pharmacol* 2007; **47**: 485–96.
- 55 Booka E, Tsubosa Y, Matsumoto T, Takeuchi M, Kitani T, Nagaoka M *et al*. Postoperative delirium after pharyngolaryngectomy with esophagectomy: a role for ramelteon and suvorexant. *Esophagus* 2017; **14**: 229–34.
- 56 Miyata R, Omasa M, Fujimoto R, Ishikawa H, Aoki M. Efficacy of ramelteon for delirium after lung cancer surgery. *Interact Cardiovasc Thorac Surg* 2017; **24**: 8–12.
- 57 Furuya M, Miyaoka T, Yasuda H, Yamashita S, Tanaka I, Otsuka S *et al*. Marked improvement in delirium with ramelteon: five case reports. *Psychogeriatrics* 2012; **12**: 259–62.
- 58 Thom R, Bui M, Rosner B, Teslyar P, Levy-Carrick N, Wolfe D *et al*. Ramelteon is not associated with improved outcomes among critically ill delirious patients: a single-center retrospective cohort study. *Psychosomatics* 2019; **60**: 289–97.
- 59 Hatta K, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C *et al*. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry* 2014; **71**: 397–403.
- 60 Nishikimi M, Numaguchi A, Takahashi K, Miyagawa Y, Matsui K, Higashi M *et al*. Effect of administration of ramelteon, a melatonin receptor agonist, on the duration of stay in the ICU: a single-center randomized placebo-controlled trial. *Crit Care Med* 2018; **46**: 1099–105.
- 61 Hov KR, Neerland BE, Andersen AM, Undseth Ø, Wyller VB, MacLulich AMJ

et al. The use of clonidine in elderly patients with delirium; pharmacokinetics and hemodynamic responses. *BMC Pharmacol Toxicol* 2018; **19**: 29.

62 Page VJ, Casarin A, Ely EW, Zhao XB, McDowell C, Murphy L *et al.* Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill

patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2017; **5**: 727–37.