The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. Informed consent for publication was obtained from the family of the patient described in the column.

Adjunctive treatment with melatonin receptor agonists for older delirious patients with the sundowning phenomenon

Ta-Chuan Yeh, MD; Chin-Bin Yeh, MD, PhD; Nian-Sheng Tzeng, MD; Wei-Chung Mao, MD

A 75-year-old man with Alzheimer dementia (Mini Mental State Examination score = 15) had been followed for 1 year. His behaviour had been well controlled with quetiapine (100 mg/d) before he was admitted to hospital with pneumonia. A fever of 39°, blood pressure of 112/70 mm Hg, heart rate of 69/min, respiratory rate of 18/min, leukocytosis (white blood cell [WBC] count $13.1 \times 10^3/\mu L$) and elevated C-reactive protein (CRP; 15.18 mg/dL) were noted at admission, but there was no obvious desaturation (SaO2 > 95%) or CO_2 retention ($Paco_2$ 42 mm Hg). During treatment with 1 gm of flomoxef administered intravenously 3 times daily for 7 days, his vital signs, laboratory data (WBC $7.6 \times 10^3/\mu L$, CRP 1.37 mg/dL) and biochemical data stabilized with resolution of chest radiographic findings on the fourth day. Despite the improvement, the patient still showed disturbed consciousness, disorientation and physical aggression that met the DSM-IV-TR diagnostic criteria for delirium. He was transferred to our psychiatric unit on the seventh day. All medication except quetiapine was discontinued to minimize drug–drug interaction.

Despite up-titrating oral quetiapine (150 mg/d) and intermittent intramuscular injections of low dose haloperidol (2.5 mg), the patient's delirium was refractory at night, manifest as interchanging oversedation and severe psychomotor agitation. His Delirium Rating Scale-Revised-98 (DRS-R-98) score was 36. We added 4 mg of ramelteon administered daily at 9 pm on the tenth day to correct his sleep–wake cycle abnormalities. On his first day taking ramelteon, the man's condition improved, with more than 6 hours of sleep, much less arousal and better daytime orientation. Owing to the persistent sundowning phenomenon (DRS-R-98 = 23), we titrated ramelteon to 8 mg on the 18th day. Over the following 3 days, the patient's scores on the subscales of DRS-R-98 improved, especially in terms of perceptual disturbances, visual hallucination, language, thought process abnormalities and attention. On the 21st day, his delirium resolved, and the final DRS-R-98 score was 10.

Delirium is an acute neuropsychiatric syndrome characterized by deranged consciousness and attention deficit with a typical fluctuating course, resulting in greater morbidity and mortality.[1] Among pharmacological interventions for delirium, antipsychotics are still recommended as a first choice,[2] but the U.S. Food and Drug Administration has noted that treating elderly patients with atypical antipsychotics is associated with serious adverse effects and increased mortality.[3,4]

Previous reports have suggested that delirium can be divided into hyperactive, hypoactive and mixed types.[5] The hyperactive type is associated with a low melatonin level and the absence of a normal melatonin secretion rhythm.[6,7] Behavioural characteristics include aggressiveness, hypervigilance, uncooperativeness and poor orientation.[8] The sleep–wake cycle–regulating effects of melatonin are probably correlated with delirium.[9] Two clinical trials have shown that exogenous low-dose melatonin administered nightly to elderly medical or elective surgical patients was successful in decreasing the incidence of delirium.[10–12]

Ramelteon demonstrated a high affinity for melatonin receptors, with a longer half-life and better efficacy in the treatment of insomnia than melatonin.[13] It has also been used to prevent delirium in a randomized controlled trial involving older patients with serious medical problems. Those receiving ramelteon (8 mg/d, n = 33) had a lower risk for delirium than those receiving placebo (n = 34, 3% v. 32%).[14] Furuya and colleagues[15] reported that five elderly patients recovered from delirium within 24 hours with ramelteon (8 mg/d) without any adverse effects, and other case series also showed the same results.[16,17]

Our patient's case illustrates the benefit of combined therapy with a melatonin agonist and an atypical antipsychotic in an older delirious patient who responded poorly to either typical or atypical antipsychotics. The modulating effects on the melatonin pathway could inhibit central dopaminergic activities and enhance nicotinic acetylcholine functions.[18,19] Current evidence from case series with a limited number of patients supports the use of ramelteon monotherapy in patients with delirium,[16,20] but atypical antipsychotics are still the first-line agents of choice to manage the condition. Adding ramelteon to atypical antipsychotics may help to manage the sundowning phenomenon quickly for older delirious patients with a refractory course. Further studies are needed to confirm its optimal dosage, duration of treatment, and its effect on brain functions.

Affiliations: From the Department of Psychiatry, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei, Taiwan (T. Yeh, C. Yeh, N. Tzeng, W. Mao); the Student Counseling Center, National Defense Medical Center, Taipei, Taiwan (N. Tzeng); and the Institute of Brain Sciences, National Yang-Ming University, Taipei, Taiwan (W. Mao).

Competing interests: None declared.

DOI: 10.1503/jpn.140166

References

1. Kiely DK, Marcantonio ER, Inouye SK, et al. Persistent delirium predicts greater mortality. *J Am Geriatr Soc* 2009; 57:55-61.
2. Friedman JI, Soleimani L, McGonigle DP, et al. Pharmacological treatments of non-substance-withdrawal delirium: a systematic review of prospective trials. *Am J Psychiatry* 2014;171:151-9.
3. Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354:1157-65.
4. Lonergan E, Britton A, Luxenberg J, et al. Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007;CD005594.
5. Liptzin B, Levkoff SE. An empirical study of delirium subtypes. *Br J Psychiatry* 1992;161:843-5.
6. Iguichi H, Kato KI, Ibayashi H. Age-dependent reduction in serum melatonin concentrations in healthy human subjects. *J Clin Endocrinol Metab* 1982; 55:27-9.
7. Olofsson K, Alling C, Lundberg D, et al. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand* 2004;48:679-84.
8. 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;24:789-856.
9. de Rooij SE, van Munster BC. Melatonin deficiency hypothesis in delirium: a synthesis of current evidence. *Rejuvenation Res* 2013;16:273-8.
10. Al-Aama T, Brymer C, Gutmanis I, et al. Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. *Int J Geriatr Psychiatry* 2011;26:687-94.
11. 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.
12. de Jonghe A, Korevaar JC, van Munster BC, et al. Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. *Int J Geriatr Psychiatry* 2010;25:1201-8.
13. Miyamoto M. Pharmacology of ramelteon, a selective MT1/MT2 receptor agonist: a novel therapeutic drug for sleep disorders. *CNS Neurosci Ther* 2009;15:32-51.
14. Hatta K, Kishi Y, Wada K, et al. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry* 2014;71:397-403.
15. Furuya M, Miyaoka T, Yasuda H, et al. Marked improvement in delirium with ramelteon: five case reports. *Psychogeriatrics* 2012;12:259-62.
16. Kimura R, Mori K, Kumazaki H, et al. Treatment of delirium with ramelteon: initial experience in three patients. *Gen Hosp Psychiatry* 2011;33:407-9.
17. Tsuda A, Nishimura K, Naganawa E, et al. Successfully treated delirium in an extremely elderly patient by switching from risperidone to ramelteon. *Psychiatry Clin Neurosci* 2013;67:130.
18. Zisapel N. Melatonin–dopamine interactions: from basic neurochemistry to a clinical setting. *Cell Mol Neurobiol* 2001;21:605-16.
19. Markus RP, Silva CL, Franco DG, et al. Is modulation of nicotinic acetylcholine receptors by melatonin relevant for therapy with cholinergic drugs? *Pharmacol Ther* 2010;126:251-62.
20. Tsuda A, Nishimura K, Naganawa E, et al. Ramelteon for the treatment of delirium in elderly patients: a consecutive case series study. *Int J Psychiatry Med* 2014;47:97-104.