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Preventive Effects of Ramelteon on Delirium: A Randomized Placebo-Controlled Trial

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IMPORTANCE No highly effective interventions to prevent delirium have been identified.

OBJECTIVE To examine whether ramelteon, a melatonin agonist, is effective for the prevention of delirium.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, rater-blinded, randomized placebo-controlled trial was performed in intensive care units and regular acute wards of 4 university hospitals and 1 general hospital. Eligible patients were 65 to 89 years old, newly admitted due to serious medical problems, and able to take medicine orally. Patients were excluded from the study if they had an expected stay or life expectancy of less than 48 hours.

INTERVENTIONS Sixty-seven patients were randomly assigned using the sealed envelope method to receive ramelteon (8 mg/d; 33 patients) or placebo (34 patients) every night for 7 days.

MAIN OUTCOMES AND MEASURES Incidence of delirium, as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).

RESULTS Ramelteon was associated with a lower risk of delirium (3% vs 32%; $P = .003$), with a relative risk of 0.09 (95% CI, 0.01-0.69). Even after risk factors were controlled for, ramelteon was still associated with a lower incidence of delirium ($P = .01$; odds ratio, 0.07 [95% CI, 0.008-0.54]). The Kaplan-Meier estimates of time to development of delirium were 6.94 (95% CI, 6.82-7.06) days for ramelteon and 5.74 (5.05-6.42) days for placebo. Comparison by log-rank test showed that the frequency of delirium was significantly lower in patients taking ramelteon than in those taking placebo ($\chi^2 = 9.83$; $P = .002$).

CONCLUSIONS AND RELEVANCE Ramelteon administered nightly to elderly patients admitted for acute care may provide protection against delirium. This finding supports a possible pathogenic role of melatonin neurotransmission in delirium.

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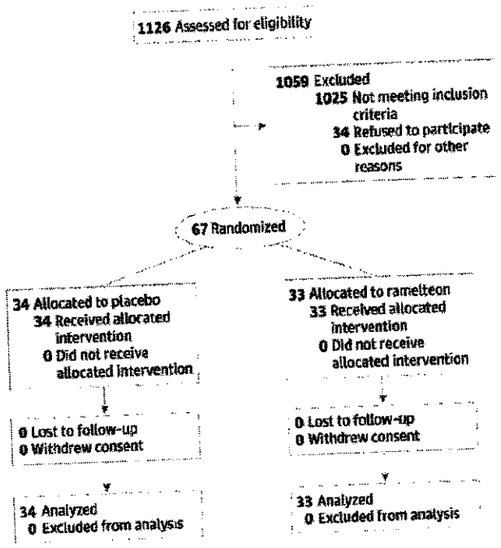
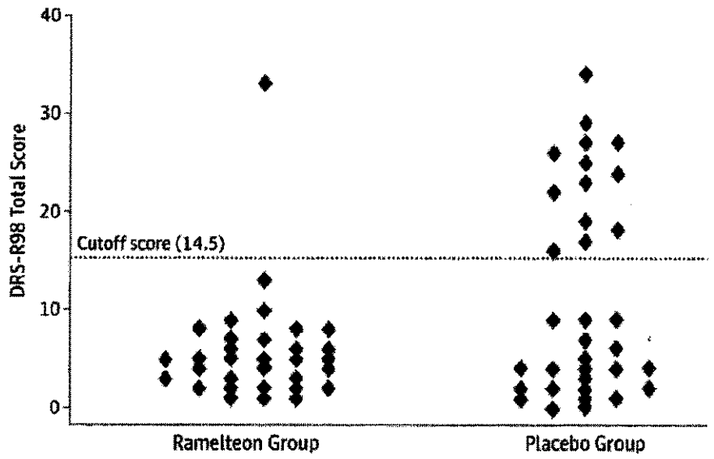


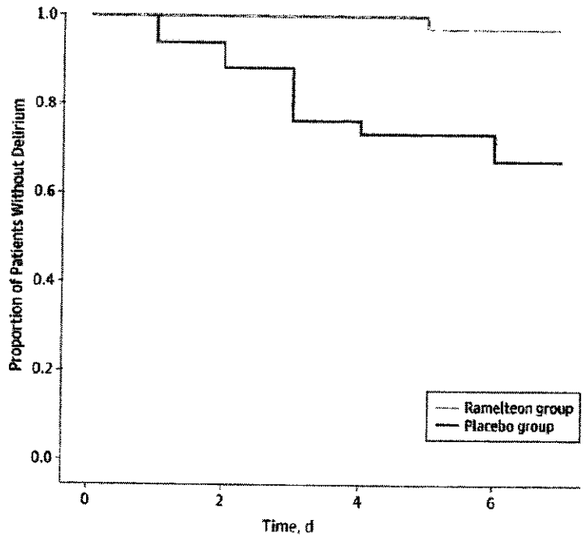
1 Figure Legend:

Trial ProfileOf 67 patients who met inclusion criteria and agreed to participate in the study, 34 were randomized to receive placebo and 33 to receive ramelteon.



2 Figure Legend:

Scattergrams of Each Patient's Highest Total Score on the Delirium Rating Scale–Revised-98 (DRS-R98) Each patient was assessed until the development of delirium or up to 7 days. The cutoff score was 14.5. However, 2 patients with dementia in the placebo group had scores of 17 and 19 but did not have a delirium diagnosis according to criteria in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).



3 Figure Legend:

Time to Development of DeliriumThe Kaplan-Meier estimates of the interval to the development of delirium were 6.94 (95% CI, 6.82-7.06) days for patients receiving ramelteon and 5.74 (5.05-6.42) days for those receiving placebo. Comparison by log-rank test showed that delirium developed significantly less frequently in the ramelteon group ($\chi^2 = 9.83$; $P = .002$).