

Following these three points, we suggest that medical care content was the core of interdisciplinary educational support for early-stage dementia patients and their family members. Finally, there is a need to continue research to verify this program's effectiveness.

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Disclosure statement

The authors declare no conflict of interest.

References

- 1 Toba K, Washimi Y, Awata S et al. *Basic Research Projects for Creating Support Services Focused on the Early Stage of Dementia*. Aichi: National Center for Geriatrics and Gerontology, 2013; 1–13.
- 2 Ministry of Health, Labour and Welfare. Outline of future direction of dementia policy .Tokyo: Japan. 2012 June [Cited 1 Sep 2013.] Available from URL: <http://www.mhlw.go.jp/topics/kaigo/dementia/dl/houkousei-02.pdf>.
- 3 De Rotrou J, Cantegreil I, Faucounau V et al. Do patients diagnosed with Alzheimer's disease benefit from a psycho-educational programme for family caregivers? A randomized controlled study. *Int J Geriatr Psychiatry* 2011; **26**: 833–842.
- 4 Hepburn KW, Tornatore J, Center B, Ostwald SW. Dementia family caregiver training: affecting beliefs about caregiving and caregiver outcomes. *J Am Geriatr Soc* 2001; **49**: 450–457.
- 5 Chien WT, Lee IYM. Randomized controlled trial of a dementia care programme for families of home-resided older people with dementia. *J Adv Nurs* 2011; **64**: 774–787.
- 6 Eloniemi-Sulkava U, Notkola IL, Hentinen M et al. Effects of supporting community-living demented patients and their caregivers: a randomized trial. *J Am Geriatr Soc* 2001; **49**: 1282–1287.
- 7 Mittelman MS, Ferris SH, Shulman E et al. A family intervention to delay nursing home placement of patients with Alzheimer disease, A randomized controlled trial. *JAMA* 1996; **276**: 1725–1731.
- 8 Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *Int Disabil Stud* 1988; **10**: 64–67.
- 9 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**: 189–198.
- 10 Baumgarten M, Becker R, Gauthier S. Validity and reliability of the dementia behavior disturbance scale. *J Am Geriatr Soc* 1990; **38**: 221–226.
- 11 Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feeling burdened. *Gerontologist* 1980; **20**: 649–655.
- 12 Suganuma N et al. Literature review of interventions for family caregivers of the elderly with dementia. *J Japan Acad Gerontol Nurs* 2012; **17**: 74–82.
- 13 Yamaguchi H. Family Caregivers' Guidebook. *Basic Research Projects for Creating Support Services Focused on the Early Stage of Dementia*. Aichi: National Center for Geriatrics and Gerontology, 2013; 88–89.
- 14 Pam O, Nancy G, Lucy B. *Responding Creatively to the Needs of Caregivers*. Tokyo: Tutsui Publishing, Inc, 2005; 52–61.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Flow chart of the study protocol.

REVIEW ARTICLE

Educational program in Japan for Dementia Support Doctors who support medical and care systems as liaisons for demented older adults in the community

Yukihiko Washimi,¹ Kentaro Horibe,¹ Akinori Takeda,¹ Takashi Abe² and Kenji Toba³

¹Department of Cognitive Disorders, National Center for Geriatrics and Gerontology, Obu, ²CEO HAM Human-Social Institute LCC, Tokyo, and ³President of National Center for Geriatrics and Gerontology, Obu, Japan

Now that the number of elderly people has increased and the number of dementia patients is rapidly increasing, dementia might be regarded as a common disease. Under these circumstances, the establishment of systems to support the elderly with dementia from the early stages, and to provide primary care doctors and care workers with necessary education is an urgent issue. Up to the end of 2012, a total of 2680 doctors had been certified as Dementia Support Doctors (DSD). The DSD's function and roles are: (i) to support primary care doctors and care specialists involved in the medical care, and general care of dementia patients; (ii) to facilitate multidisciplinary cooperation led by a Community General Support Center; and (iii) to give lectures about dementia to primary care doctors and educate people in the community. DSD are more skilled than primary care doctors in the following functions: differential diagnosis; outpatient services to deal with behavioral and psychological symptoms of dementia; community liaison; and home care. *Geriatr Gerontol Int* 2014; 14 (Suppl. 2): 11–16.

Keywords: community liaison, Dementia Support Doctor, educational program for Dementia Support Doctors.

Introduction

Now that the number of patients with dementia is rapidly increasing with the increase of the number of elderly people, dementia might be regarded as a common disease. In fact, primary care doctors are now more frequently engaged in the care of patients with dementia, regardless of their specialty, and, consequently, it has become necessary for all of them to have a certain level of ability to treat the disease. Furthermore, in dementia care, appropriate role-sharing among medical professionals is important, while it is necessary to cooperate with care workers and administrative institutions.¹ Under these circumstances, the establishment of systems to support the elderly with dementia from the early stages, and provide primary care doctors and care workers with the necessary education is an urgent issue. To address this, the Ministry of Health, Labor, and Welfare launched a plan in 2005 to train Dementia Support Doctors (DSD), playing a central

role in community-based activities to support dementia patients. Subsequently, in 2006, another plan called the Skill-up Program of Dementia Medicine for Primary Care Doctors was initiated mainly by DSD, and, up to the end of 2012, a total of 2680 doctors had been certified as DSD. The total number of doctors who had completed the Skill-up Program of Dementia Medicine for Primary Care Doctors by the end of 2011 was 28 024. The government aims to increase the number of DSD to 4000, and that of doctors who have completed the Skill-up Program of Dementia Medicine for Primary Care Doctors to 50 000 by 2017.² The present article reports appropriate DSD training systems, while discussing the roles and activities of DSD. It also provides an outline of training programs focusing on long-term care services.

Educational program for DSD

With a Grant for Plans to Promote Health and Medical Services for the Elderly, the Ministry of Health, Labor, and Welfare launched the Research Project on Community Systems to Provide Early Identification and Appropriate Care for the Elderly with Dementia in 2004. In line with this, a working group was organized to examine methods to provide the Skill-up Program of Dementia Medicine for Primary Care Doctors,³ with a

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Correspondence: Dr Yukihiko Washimi MD PhD, Department of Cognitive Disorders, National Center for Geriatrics and Gerontology, Obu, Aichi 474-8511, Japan. Email: washimi@ncgg.go.jp

view to discussing the content of such training, as well as methods and systems to cooperate with doctors specializing in dementia care, who support Primary Care Doctors' medical practice and roles in the community. The DSD Training Program was initiated in 2005, and the Skill-up Program of Dementia Medicine for Primary Care Doctors in 2006. The former, aiming to train DSD who provide primary care doctors with advice regarding the early diagnosis of dementia, and play a central role in dementia care, was initially led by the National Center for Geriatrics and Gerontology as a commissioned business. In 2005, training materials, such as texts and DVDs, were developed, and, in 2006, training seminar sessions took place in Sapporo, Tokyo, Fukuoka and Obu (twice), producing a total of 318 DSD (covering 44 prefectures and 13 ordinance-designated cities). Following this, five seminar sessions a year have been held mainly in Tokyo, Nagoya, Osaka or Kyoto, and Fukuoka. Those who want to participate in these sessions should be recommended by the medical associations located in relevant ordinance-designated cities or their prefectures. Although those with medical associations' recommendation initially accounted for the majority, an increasing number of participants in recent years have made requests for participation to the medical associations located in ordinance-designated cities or their prefectures. To follow changes in clinical trial methods and systems, and reflect participants' opinions, training texts have been revised every year; up to 2012, four versions had been published. A major revision took place in 2012, and, in 2013, new texts have been adopted. The purposes of such revisions include: to focus on DSD-specific issues more closely, rather than conventional primary care doctor training; to provide the latest information regarding diagnosis and treatment; to increase sections related to medical liaison

systems in order to enhance participants' understanding of the importance of cooperation between medical and care professionals when supporting the elderly with dementia requiring long-term care; and to promote case studies and discussions. Each training session takes place from a Saturday afternoon to the following Sunday morning. In addition to learning methods to teach primary care doctors the content of each domain, participants are provided with lectures regarding the importance of DSD and primary care doctor training programs by an officer invited from the Office for Dementia and Elder Abuse Prevention, the Ministry of Health, Labor, and Welfare, and officers invited from the Japan Medical Association. Participants also freely discuss challenges for DSD in the establishment of systems to facilitate the early diagnosis and treatment of dementia in the community. By promoting discussions among doctors based in different areas, it is possible to clarify the status of each area's approach and points for improvement.

Current status and challenges of DSD

The roles of DSD include: (i) supporting primary care doctors and care professionals engaged in dementia care; (ii) establishing multiprofessional liaison systems led by the Community General Support Center; and (iii) giving lectures about dementia-specific training for primary care doctors and education for residents. In short, it is expected that DSD will promote cooperation between different medical professions, and between medical and care professions. (Fig. 1) As previously mentioned, the current total number of DSD is 2680; those specialized in fields generally related to dementia, such as psychiatry, neurology, geriatric medicine and neurosurgery, account for 42%, and those specialized in

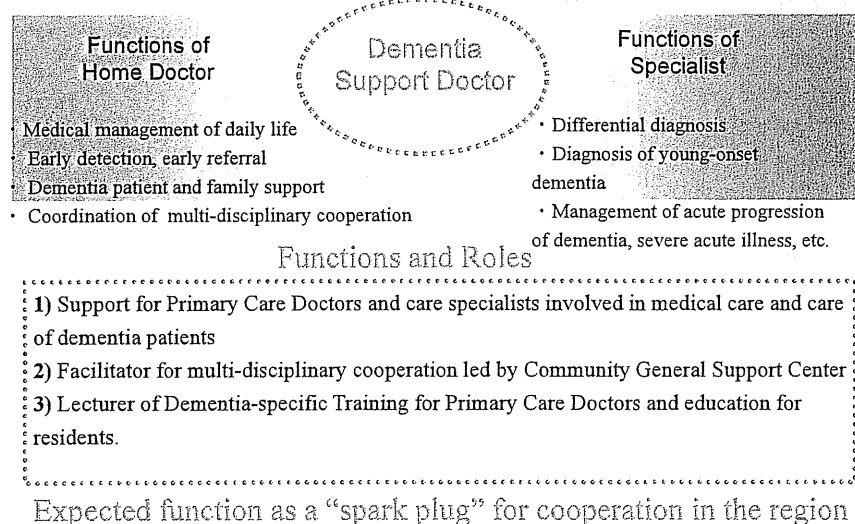


Figure 1 Functions and roles of Dementia Support Doctor.

[n=957] Questionnaire to 1,974 Dementia Support Doctors undergoing training between 2005-2011

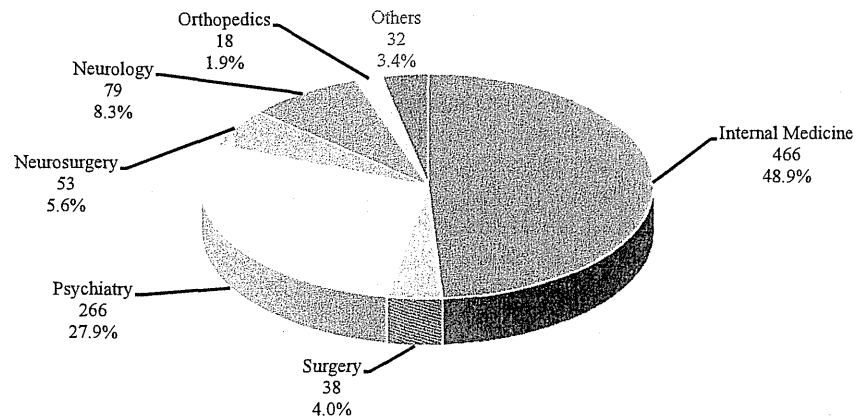


Figure 2 Breakdown of clinical departments of Dementia Support Doctors.

other fields of internal medicine, orthopedics, and urology account for 58%. Although DSD of the former group are frequently required for specialized medical services, such as the differential diagnosis of dementia, diagnosis of early-onset dementia, and treatment of advanced symptoms and severe somatic complications, those of the latter group are frequently required for primary care doctor functions, such as daily medical management, early identification and treatment of diseases, patient and family support, and multiprofessional cooperation. Considering that the necessary DSD functions also vary among different areas, it has been pointed out that the roles of DSD are unclear. According to a survey carried out from January to February 2011 involving DSD-related departments of a total of 66 municipalities, including 47 prefectures and ordinance-designated cities, those with 10–19 DSD accounted for the majority (24), followed by those with 30 or more (13) and those with fewer than 10 (16).⁴ The number of DSD was highest in Tokyo (284), followed by Chiba (88) and Hiroshima (72). Support for The Skill-up Program of Dementia Medicine for Primary Care Doctors was available in 95.5%, and education for residents was provided in 48.5%, whereas community liaison systems were not established, or their establishment was uncertain in 60%. As a reason for the latter, a large number of municipalities answered that community liaison was regarded as part of community-based activities, and they were not actively engaged in them; this shows that administrative bodies might not have been involved in the establishment of community liaison systems. Furthermore, information regarding accessibility to DSD in each area is important; however, DSD lists were available to the Community General Support Center in 70%, to residents in 50% and not available in 30% of all areas. Regarding networks among DSD, broad area networks

(the metropolitan area and districts) had been established in 14 (21.5%), and local networks (local demographic division of medical services where the DSD gives medical care) had been established in 12 (18.5%) areas. In 2012, a direct questionnaire survey was carried out to clarify the status of DSD,⁵ involving 1974 doctors who had completed the training program within the period between 2005 and 2011. The questionnaire sheet was distributed by mail, and 957 responded (response rate: 48.5%). Respondents were specialized in: internal medicine (48.9%), psychiatry (27.2%) and neurology (8.3%). Specialists certified by dementia-related academic associations accounted for 41.4% (Fig. 2). Their daily DSD activities included: (i) medical care for dementia patients (904: 94.5%); (ii) medical and multiprofessional liaison activities (804: 84.0%); and (iii) training and education (614: 64.2%; Fig. 3). The contents of (i) included treatment (96.9%), early identification (88.9%) and diagnosis (87.3%), nearly 90% of all DSD were carrying out these activities daily. A liaison system had been established with residents in 87.4%, long-term care support specialists in 78.0%, and the Community General Support Center in 73.9%; nearly 80% answered that a liaison system had been established. In contrast, a liaison system with primary care doctors had been established at a relatively low rate of 65.9%. The respondents participated in the planning and development of training and educational programs, such as dementia-specific training for primary care doctors (83.1%), multiprofessional training (79.3%) and educational seminars for residents (83.4%). These activities were carried out daily by approximately 80% of all DSD. These results suggest that individual DSD might be carrying out activities, such as medical services, liaison activities and education, daily in general; however, a liaison system with primary care doctors,

[n=957] Responses from 1,974 who completed DSD training program between 2005 and 2011

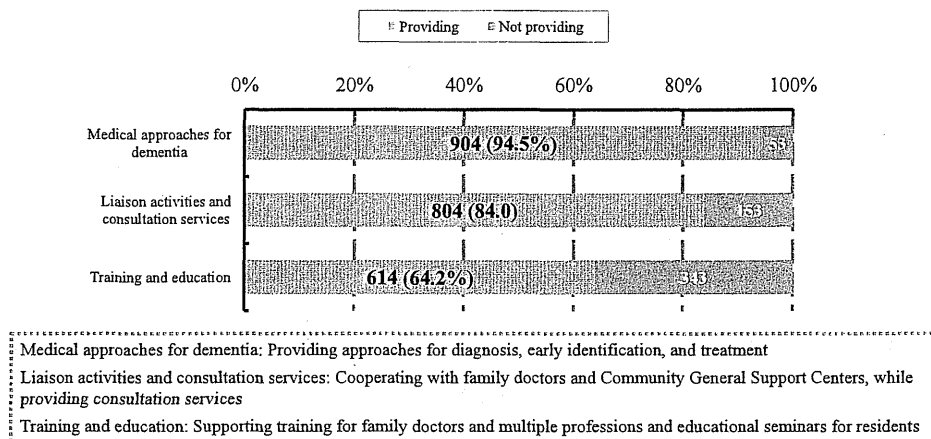


Figure 3 Activities of Dementia Support Doctors.

compared with residents and the Community General Support Center, had been established less frequently, showing the necessity of promoting and improving approaches in this respect. Regarding the large number of DSD (and medical institutions) as available resources, it might be necessary to sufficiently utilize them as a medical base supporting residents, care providers and primary care doctors engaged in dementia care. It might also be necessary to discuss and determine their roles, functions, and directionality in consideration of the statuses of related medical fields and association-certified specialists. In order to appropriately utilize DSD in the community, the municipalities' and Community General Support Centers' understanding is indispensable; in line with this, it might be desirable to develop community systems, while discussing appropriate methods to promote DSD activities, including grants for comprehensive dementia support plans among municipalities, Community General Support Centers and medical associations.

Awata carried out a study using the Medical Service Questionnaire Sheet for Dementia to evaluate the ability of general clinics located in the Tokyo metropolitan area to deal with dementia, and reported that medical institutions with doctors who had completed The Skill-up Program of Dementia Medicine for Primary Care Doctors showed a significantly greater ability than those without this training in the following respects: primary care doctor functions; differential diagnosis; outpatient services to deal with behavioral and psychological symptoms of dementia; community liaison; and home care.⁶ He also pointed out that medical institutions with DSD showed even higher levels of these functions (Fig. 4).

To promote liaison among DSD, and provide a basis for their information exchange, a portal site named the DSD Network (<http://www.dsd-network.jp>) was launched in May 2011, with a Grant for Geriatric Medicine Research and Development. The contents shown in Table 1 are viewable on this site, with a view to facilitating DSD activities. As another approach to support DSD, follow-up training programs have been used in some areas since 2009 to provide the DSD with opportunities to acquire new knowledge and learn other areas' approaches. In addition, as described in the following section, multiprofessional simulation conferences are being planned to enhance the knowledge of long-term care and liaison systems.

Long-term care training programs for doctors

In dementia care, it is essential to have a viewpoint based on a daily living activity model, in addition to a medical model. In other words, dementia care aims to improve patients' quality of life, rather than providing treatment and life-saving approaches, and focuses on disabilities (maintenance of activities of daily living), rather than diseases (maintenance of a normal physiological state). In line with this, it might be necessary to establish appropriate systems to provide team-based approaches with cooperation from multiple professions, as well as medical professionals. Honma pointed out that it is not reasonable to draw a line between medical and long-term care services when supporting dementia patients, and it is necessary to share knowledge and ideas among all those involved in dementia care, based

Dementia Support Doctors in Japan

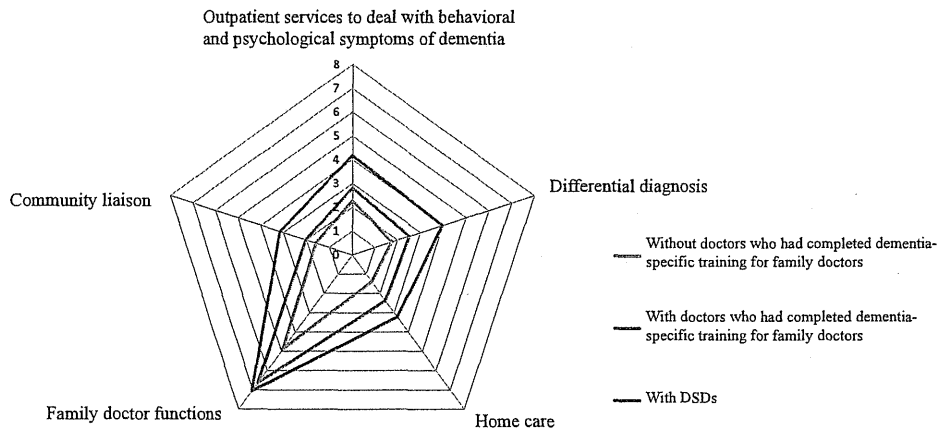


Figure 4 Outcomes of Dementia Support Doctors (DSD) and dementia-specific training programs for primary family doctors.

Table 1 Contents of the Dementia Support Doctors portal site

Category 1	Examples of community-based activities
Contents	
	Nagata-ku, Kobe City, Tokyo Metropolitan Area, Nagoya City, Shiga Prefecture, Nagano Prefecture
Category 2	Dementia-related issues
Contents	
	Roles of DSD: Development of new dementia guidelines, vascular dementia, development of neuroimaging for diagnosis of dementia, dysphagia due to dementia, non-pharmacological therapies, treatment of delirium, early-onset dementia (presenile dementia)
	Status of long-term care insurance systems (under commission), status of medical centers specialized in dementia care
Category 3	Materials, texts and DVDs previously used for DSD training
Category 4	List of DSD (by prefecture)
Category 5	Case studies
Category 6	Activities of academic study groups

DSD, Dementia Support Doctors.

on common training programs; however, such programs have not yet been developed.⁷ Furthermore, although study visits to long-term care facilities and nursing training programs have already been adopted in some medical schools as part of education regarding long-term care, these approaches are completely insufficient. Considering that Japan is becoming a super-aged society, this might be a serious problem, requiring prompt solutions.

Conclusion

Increasing the numbers of medical and care professionals specializing in dementia, and establishing systems to provide them with necessary education is urgently required.

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Disclosure statement

The authors declare no conflict of interest.

References


- 1 Washimi Y. Care and medical support for the person with Alzheimer's disease. *J Clin Exp Med* 2007; 220: 456-462.
- 2 Ministry of Health, Labour, and Welfare. Five-year plan for the promotion of dementia care (orange plan). 2012.

- 3 Japan Public Health Association. Report of the study group for the development of primary care doctor training programs to deal with an increasing number of dementia patients, 3, 2004.
- 4 Silver Age Institute. Report of a research project for the development of dementia support doctor follow-up training programs. 53–67, 2011 [Cited 31 March 2011.] Available from URL: http://www.silver-soken.com/jisseki/html/h22_support.html
- 5 NLI Research Institute. Report of a research project on the roles of dementia support doctors and systems and educational materials to train them. pp. 36–39, 2013.
- 6 Awata S. Functions of doctors working in clinics – significance of community-based support activities in dementia care-. *Geriatr Med* 2013; **151**: 35–38.
- 7 Honma A. Status and challenges of dementia-related education and future perspectives. *Jpn J Geriatr Psychiatry* 2010; **21**: 1116–1118.

Original Investigation

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

Kotaro Hatta, MD, PhD; Yasuhiro Kishi, MD, PhD; Ken Wada, MD, PhD; Takashi Takeuchi, MD, PhD; Toshinari Odawara, MD, PhD; Chie Usui, MD, PhD; Hiroyuki Nakamura, MD, PhD; for the DELIRIA-J Group

 Editorial page 364

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.

TRIAL REGISTRATION University Hospital Medical Information Network Clinical Trials Registry Identifier: UMIN000005591

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the DELIRIA-J Group are listed at the end of this article.

Corresponding Author: Kotaro Hatta, MD, PhD, Department of Psychiatry, Juntendo University Nerima Hospital, Takanodai 3-1-10, Nerima-ku, Tokyo 177-8521, Japan.

Delirium represents an acute change in cognition with altered consciousness and impaired attention that fluctuates over time.¹ The prevalence of delirium is 11% to 33% on admission, and the incidence during hospitalization is 3% to 56% among elderly patients presenting to emergency departments or medical and surgical wards in general hospitals.²⁻⁵ With the increase in the aged population, further increases in delirium seem likely. However, no medications against delirium have yet been approved. Delirium prevention has been investigated in several randomized clinical trials (RCTs). Based on a single RCT, programs for proactive geriatric consultation may reduce the incidence and severity of delirium in patients undergoing surgery for hip fracture.^{6,7} In contrast to the lack of efficacy of cholinergic enhancement in preventing delirium,⁸⁻¹⁰ some benefits of antipsychotics have been shown.¹¹⁻¹³ However, physicians may hesitate to use antipsychotics for delirium prevention given the risk of adverse effects.

Melatonin, a pineal gland hormone that regulates the sleep-wake rhythm, is reportedly associated in an RCT with a lower risk of delirium.¹⁴ Ramelteon, an agonist of melatonin that has been approved by the US Food and Drug Administration for the treatment of insomnia characterized by difficulty at sleep onset, has been suggested as an option for preventing delirium in case series.¹⁵⁻¹⁷ We examined whether ramelteon has effects in preventing delirium in elderly patients.

Methods

Setting and Participants

This randomized placebo-controlled trial was conducted from September 1, 2011, through October 31, 2012, in 4 university hospitals and 1 general hospital. All study protocols were approved by the institutional review board at each site, and written informed consent was obtained from patients or their proxy decision makers. This activity was conducted by the DELIRIA-J (Delirium Intervention Research for Improving Acute phase outcomes in Japan) study group.

Eligible patients were 65 to 89 years old, newly admitted due to serious medical problems, and able to take medicine orally. Patients were admitted via emergency departments to intensive care units or regular acute wards. Patients were excluded from the study if they had an expected stay or life expectancy of less than 48 hours.

The observation period was 1 week, and we considered that it would be difficult during such a short time to discriminate between delirium and cognitive fluctuation in certain diseases, such as severe liver dysfunction or Lewy body disease. Patients with such diseases were therefore excluded in advance.

Fluvoxamine is known to interact with ramelteon as a major interaction. Withdrawal syndromes associated with alcohol dependency and drug abuse can include delirium, obviously differing etiologically from delirium caused by systemic diseases. Patients with psychotic or bipolar disorders are usually receiving treatment with antipsychotics, which may prevent the development of delirium. Patients with other mood

disorders are also often treated with antipsychotics, so they were also excluded. Patients were approached before the first night after admission; those who were already delirious at admission were excluded.

Randomization and Intervention

We intended to perform this RCT in emergency situations. Although double blinding is ideal, we supposed that the participation rate of patients with such a design would have been much lower than with single blinding. The lower the participation rate, the less representative the results would be for real-world practice. We therefore chose to use only rater blinding. Patients were randomized using the sealed envelope method in a rater-blind manner to receive either ramelteon or placebo. For randomization, we referred to a random number table, with sequentially numbered, opaque, sealed envelopes used to conceal the allocation sequence. Study medication was managed by nurses and administered daily at 9 PM. This regimen was continued until the development of delirium or up to 7 days. The physician in charge kept the randomization code, and no rater became aware of treatment allocations until requesting unmasking on December 12, 2012.

Nurses were blinded except those who managed the study medication. Nurses provided all patients equally with preventive care, such as avoidance of immobilization, adequate lighting, noise reduction, on-time clocks and calendars, and regular verbal communication. Other staff, such as physiotherapists, were blinded. Family members were not allowed to stay in hospitals after 8 PM, and study medication was given at 9 PM. Therefore, there was low likelihood of bias due to interactions with family members. Thus, neither nursing care nor family interactions could have been different in the ramelteon group.

The dosage of ramelteon was 8 mg/d, given as a single tablet nightly, representing the standard dosage for the approved indication of sleep disturbance. The placebo comprised 330 mg of lactose powder. The placebo did not match the ramelteon active agent in appearance. This was a shortcoming of the study, but we considered that this drawback would have little effect on the development of delirium, which is characterized by impaired consciousness, including attention and awareness.

We had to select an as-needed drug for patients who would show insomnia and require a sleeping pill because we intended to perform the trial in real-world practice. We discussed which drug would be optimal for this purpose among trazodone, zolpidem, zopiclone, and hydroxyzine. Trazodone is often used to treat delirium in Japan because Japanese researchers have reported a case series showing the efficacy of trazodone against delirium.¹⁸ The effects of trazodone could thus have masked the preventive effects of ramelteon.

Although zolpidem and zopiclone are not listed in the Beers criteria,¹⁹ the Japanese package inserts for these drugs list adverse effects including delirium, confusion, hallucinations, excitement, disinhibition, aggression, abnormal behavior, and twilight state. In practice, we sometimes encounter elderly patients with delirium induced by these drugs. In contrast, we have seldom encountered elderly patients with delirium induced by hydroxyzine. We therefore suppose that zolpidem

and zopiclone could have exaggerated differences in outcome between the active and placebo arms more than hydroxyzine, and would be less ethical to prescribe than hydroxyzine owing to the higher risk of inducing delirium, based on our experience.

Because hydroxyzine is approved by the Ministry of Health, Labour and Welfare in Japan, all institutional review boards approved its use for such purposes. Hydroxyzine reportedly has low affinity for muscarinic receptors (mean [SD] inhibition constant [K_i], 3800 [100] nmol/L) in the bovine cerebral cortex.²⁰ The pharmaceutical company producing hydroxyzine (Atarax; Pfizer Japan Inc) informed us that they had no human data on the K_i values of hydroxyzine for the muscarinic receptor because it was an old drug. Data on inhibition constants of hydroxyzine for muscarinic acetylcholine receptors in humans thus seem to be lacking. Although the Beers criteria¹⁹ listed hydroxyzine as a strong anticholinergic drug, available data indicate that it has weak anticholinergic effects. We thus chose it as an as-needed drug for patients with insomnia who required a sleeping pill, with a nightly dose limit of 25 mg, as needed for insomnia.

Outcomes and Measurements

Before starting the trial, site coordinators were trained to assess outcomes as raters. All site coordinators were experienced psychiatrists. At the time of admission, baseline characteristics were collected. Acute Physiology and Chronic Health Evaluation II (APACHE II)²¹ scores and the Charlson Comorbidity Index²² were also assessed to evaluate physical condition. The Eastern Cooperative Oncology Group performance status²³ was assessed to evaluate how the disease affected activities of daily living in patients. The Clinical Dementia Rating was assessed to evaluate the existence and severity of dementia.²⁴ The Delirium Rating Scale-Revised-98 (DRS-R98) was assessed to measure delirium symptoms (Paula T. Trzepacz, MD, José R. Maldonado, MD, Jacob Kean, PhD, Malene Abell, BS, and David J. Meagher, MD, MRCPsych, unpublished data, 2010). The APACHE II scores, performance status, and DRS-R98 scores were determined daily up to 7 days. The DRS-R98 score was determined between 10 and 11 AM in all patients. Once delirium occurred, the cause was recorded according to the Delirium Etiology Rating Checklist.²⁵

The primary outcome measure was incidence of delirium, defined according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).¹ Simultaneously, we censored patients in whom delirium developed, using the DRS-R98 total score, with a cutoff score of 14.5, established for the Japanese population by investigating the reliability and validity of the Japanese version of the DRS-R98.²⁶

Raters reviewed all nursing records before morning rounds and collected information about each patient directly from bedside nurses. Raters then assessed each patient to determine whether delirium had occurred. Raters also made their rounds every afternoon. Although delirium waxed and waned, there was little risk of missing its occurrence under such close observation. Adverse events, such as somnolence, dizziness, and fatigue, were observed. Sleep metrics, such as difficulty falling and staying asleep, waking too early, poor sleep quality,

number of awakenings per night, sleep duration, and disturbance of the natural sleep-wake rhythm during study drug administration were analyzed based on patient reports, nursing observations and records, and rater observations.²⁷

Statistical Analysis

Data were collected on standardized forms and statistical analyses were performed using SPSS, version 20-J, software (IBM Japan). Differences between categorical variables in patient demographics and clinical characteristics were calculated by using Fisher exact tests. Differences between sequential variables were calculated by using unpaired *t* tests (with Welch correction if applicable). If data were not sampled from gaussian distributions, a nonparametric test (Mann-Whitney test) was used. Kaplan-Meier curves were used to estimate the probability of delirium at 7 days. We constructed multivariate logistic regression models to control for risk factors in estimating independent associations between the effects of ramelteon and the outcome of delirium as an exploratory analysis. All statistical tests were 2 tailed. Differences were considered statistically significant at $P < .05$.

The incidence of delirium during hospital stays reportedly ranges between 3% and 56%.⁵ Although patients with risk factors for delirium (eg, old age and dementia) are increasingly encountered in general hospitals, we thought that 56% was too high an incidence of delirium during general hospital stays in Japan. We therefore assumed that the incidence of delirium in patients receiving placebo would be half the upper limit (ie, 28%) and the incidence in those receiving ramelteon would be the lower limit (3%). To enable detection of differences, we set the statistical power as $1 - \beta = 80\%$ and the sensitivity as $\alpha = 5\%$. Through power analysis, we consequently set the required number of patients at 32 patients per group.

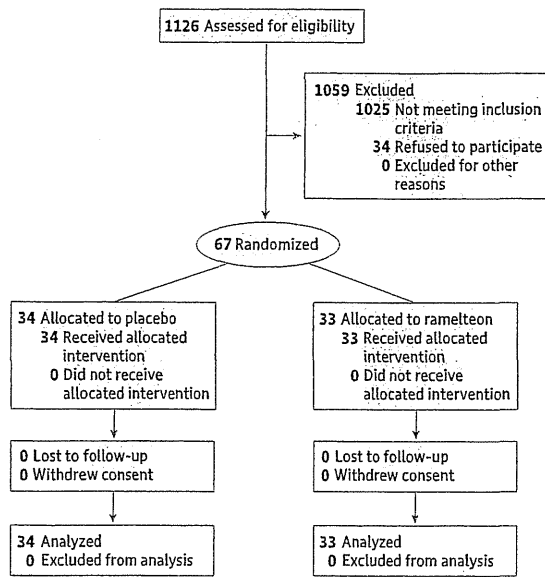
Results

During the study period, 1126 patients were assessed for eligibility; 1059 were excluded. Of the 697 patients admitted to intensive care units, 658 were intubated or had a life expectancy of less than 48 hours, and 306 of the 429 patients admitted to regular acute wards had an expected stay of less than 48 hours. Diagnoses of severe liver dysfunction, Lewy body disease, alcohol dependency, psychotic disorder, or bipolar disorder accounted for exclusion of 61 patients. As a result, 1025 patients did not meet the inclusion criteria. In addition, 3 patients admitted to intensive care units and 31 admitted to regular acute wards refused to participate.

Thus, 67 patients (24 admitted to intensive care units and 43 admitted to regular acute wards) were included in the study. Figure 1 shows the trial profile. The 67 patients were randomly assigned to the 2 treatment groups (Figure 1). The rate of study participation among eligible patients was 66% (67 of 101). No patients withdrew consent, and all were therefore included in the final analysis. Baseline characteristics of randomized patients were much the same in both groups (Table 1).

Table 2 shows outcomes. Five patients in the placebo group and 8 in the ramelteon group were discharged before 7 days,

Figure 1. Trial Profile



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

but none were discharged within 48 hours after admission. One patient in the placebo group discontinued the study drug owing to worsening of pneumonia, which was the admitting diagnosis. Six patients (18%) in the placebo group and 8 (24%) in the ramelteon group discontinued the study drug without delirium before 7 days. No significant difference in rate was seen between groups ($P = .56$). Delirium occurred in 11 patients in the placebo group and 1 patient in the ramelteon group. Figure 2 shows scattergrams of the highest total DRS-R98 score in each patient. Two patients with dementia in the placebo group with scores of 17 and 19 did not have a diagnosis of delirium according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).¹ 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). No adverse events potentially attributable to the study drug were observed.

As shown in Table 2, 3 patients (9%) in the placebo group and 6 (18%) in the ramelteon group received hydroxyzine (as needed), with no significant difference in the rate of use between groups. Delirium developed in only 1 of these 9 patients, a patient from the placebo group. Even when we excluded patients who received hydroxyzine, the rate of delirium was significantly lower in the ramelteon group than in the placebo group (4% [1 of 27 patients] vs 32% [10 of 31]; $P = .007$).

Age, diagnosis of dementia, and history of delirium are known risk factors for delirium. Among patients without a history of delirium, the rate of delirium was significantly lower in the ramelteon group than in the placebo group (0% [0 of 29 patients] vs 30% [10 of 33]; $P = .001$), suggesting that ramelteon is effective in preventing delirium in patients without any history of it. Among patients with a history of delirium, there

was no significant difference in the rates of delirium between the ramelteon and placebo groups (25% [1 of 4 patients] vs 100% [1 of 1]; $P = .40$), suggesting that the number of patients was too small to analyze.

As shown in Table 1, although no significant difference in the rate of infection was identified between the ramelteon and placebo groups, the P value for this difference was the lowest for all admission diagnoses. We thus constructed multivariate logistic regression models to control for the effects of risk factors (eg, age, diagnosis of dementia, and admission diagnosis of infection) on the estimate of an independent association between ramelteon effects and the outcome of delirium. Even after we controlled for those risk factors, ramelteon was still associated with a lower incidence of delirium ($P = .01$; odds ratio, 0.07 [95% CI, 0.008-0.54]).

Kaplan-Meier estimates of the 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 (Figure 3). Comparison by log-rank test showed that delirium developed significantly less often among patients taking ramelteon than among those taking placebo ($\chi^2 = 9.83$; $P = .002$).

Outcomes of sleep metrics during study drug administration are shown in Table 2. Unexpectedly, there were no apparent significant differences between groups in any items.

Discussion

The present finding that acutely ill elderly patients receiving ramelteon were at lower risk of delirium than those receiving placebo (3% vs 32%) is remarkable because the effect seems to exceed that previously reported for melatonin (12% for melatonin vs 31% for placebo).¹⁴ In vitro studies have demonstrated that ramelteon has 6-fold and 3-fold higher affinities for melatonin receptors 1 and 2 (MT_1 and MT_2), respectively, compared with melatonin.²⁸ The ramelteon dose in the current study was 8 mg, compared with 0.5 mg for melatonin in the previous study. Therefore, with respect to affinities for MT_1 and MT_2 receptors, ramelteon in the current study was 96-fold and 48-fold more potent, respectively, than melatonin in the previous study, which may explain its superiority in preventing delirium.

These findings suggest that reduced frequency of delirium is associated with higher affinities for the MT_1 and MT_2 receptors, supporting a possible pathogenic role of melatonin neurotransmission in delirium. The MT_1 receptor reportedly mediates acute inhibition of firing from the suprachiasmatic nucleus by melatonin,²⁹ and activity at the MT_2 receptor has been associated with the phase-shifting effects of melatonin on circadian rhythms.³⁰ Among speculated causes of delirium, such abnormalities mediated by melatonin neurotransmission might be clinically important, particularly for delirium prevention.

A strong decline in melatonin levels during aging has been consistently reported by many investigators.³¹ Among older adults with chronic insomnia, ramelteon at both 4 and 8 mg reportedly produced significant sleep-promoting activity, as indicated by polysomnographically recorded reductions of latency to persistent sleep, prolongation of total sleep time, and

Table 1. Baseline Patient Characteristics

Characteristic	Placebo Group (n = 34)	Ramelteon Group (n = 33)	P Value
Age, mean (SD), y	78.3 (6.8)	78.2 (6.6)	.92
Male sex, No. (%)	11 (32)	16 (48)	.22
Body mass index, mean (SD) ^a	21.7 (4.1)	22.6 (3.3)	.38
Habitual use of alcohol, No. (%)	4 (12)	4 (12)	>.99
Habitual use of sleeping pills, No. (%) ^b	7 (21)	7 (21)	>.99
Other prescribed medications, No. (%)			
Opioids	0	0	...
Corticosteroids	0	1 (3)	.49
Antipsychotics	0	0	...
Previous delirium, No. (%)	1 (3)	4 (12)	.20
Dementia, No. (%)	8 (24)	5 (15)	.54
Admission diagnosis, No. (%)			
Stroke	9 (26)	12 (36)	.44
Infection	8 (24)	4 (12)	.34
Fracture	8 (24)	6 (18)	.77
Heart failure/myocardial infarction	5 (15)	3 (9)	.71
Other	4 (12)	8 (24)	
Medical or surgical comorbid conditions, mean (SD), No.	1.4 (1.3)	1.3 (1.2)	.79
Index or score, mean (SD)			
Charlson Comorbidity Index	2.6 (2.2)	3.2 (2.4)	.29
APACHE II score	14.6 (2.9)	13.5 (2.8)	.12
Performance status	3.4 (0.8)	3.2 (0.8)	.31
Clinical Dementia Rating	0.6 (0.9)	0.5 (0.7)	.60
DRS-R98	4.7 (4.5)	3.5 (2.9)	.19

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; DRS-R98, Delirium Rating Scale-Revised-98.

^a Body mass index was calculated as weight in kilograms divided by height in meters squared.

^b The sleeping pills taken habitually were all benzodiazepines, including brotizolam (7 patients), etizolam (2 patients), nitrazepam (2 patients), and lormetazepam, flunitrazepam, and alprazolam (1 patient each).

Table 2. Clinical Outcomes During Study Drug Administration

Outcome	Placebo Group (34 Patients)	Ramelteon (33 Patients)	P Value
Delirium, No. (%)	11 (32)	1 (3)	.003
Worst DRS-R98 score, mean (SD)			
Without delirium	5.0 (4.9)	4.9 (2.8)	.94
With delirium	24.6 (5.0)	33	
Discontinuation of study drug without delirium before 7 d, No. (%)	6 (18)	8 (24)	.56
Due to discharge	5 (15)	8 (24)	.37
Due to worsening of medical disease	1 (3)	0	>.99
Worst APACHE II score, mean (SD)	15.0 (2.8)	14.3 (2.7)	.36
Worst performance status score, mean (SD)	3.4 (0.8)	3.2 (0.8)	.35
Use of as-needed hydroxyzine for insomnia, No. (%) ^a	3 (9)	6 (18)	.30
Adverse event potentially attributable to study drug	0	0	...
Sleep parameters, No. (%) ^b			
Difficulty falling asleep	14 (41)	10 (30)	.45
Difficulty staying asleep	14 (41)	14 (42)	>.99
Waking too early	5 (15)	7 (21)	.54
Poor sleep quality	19 (56)	21 (64)	.62
Disturbance of natural sleep-wake rhythm	3 (9)	7 (21)	.19
Awakenings per night, mean (SD)	1.6 (1.2)	1.3 (1.6)	.28
Sleep duration, mean (SD), h	6.3 (1.6)	6.3 (1.6)	.67

Abbreviations: See Table 1.

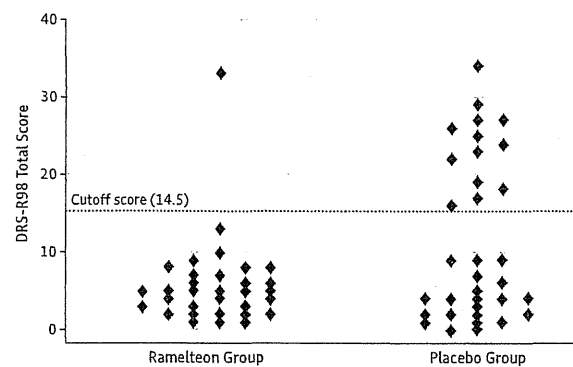
^a Only 25 mg hydroxyzine per night was allowed, as needed. In the placebo group, 1 patient received hydroxyzine for 3 nights in 6 days, and 2 for 1 night in 7 days. In the ramelteon group, 1 patient received hydroxyzine for 3 nights in 7 days and 1 for 2 nights in 7 days; the remaining 4 patients received hydroxyzine for 1 night in 7 days.

^b For sleep parameters, the presence or absence of symptoms in each patient was determined according to the dominant category during study drug administration. The frequency and duration for each patient were determined by using mean values during study drug administration. Data were excluded for the night on which delirium occurred.

improvements in sleep efficiency.³² Although our present findings did not suggest any benefit of ramelteon for sleep parameters (Table 2), larger samples are needed to statistically differentiate drug from placebo in studies based on self-report

compared with polysomnographic studies.³³ From the current findings, it is therefore unclear whether the preventive effects of ramelteon on delirium are associated with its sleep-promoting activity.

Figure 2. Scattergrams of Each Patient's Highest Total Score on the Delirium Rating Scale-Revised-98 (DRS-R98)



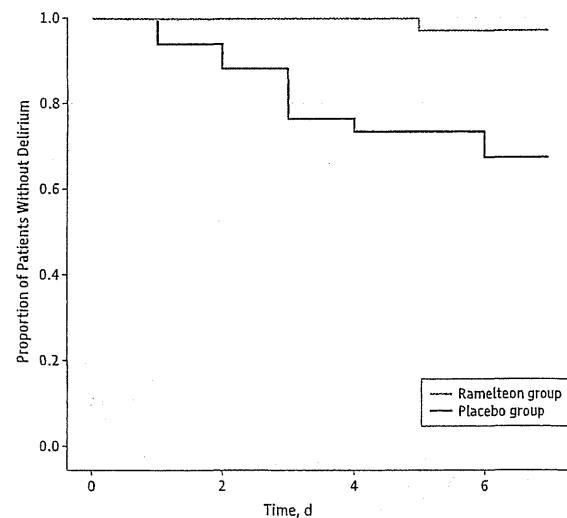
Each patient was assessed until the development of delirium or up to 7 days. The cutoff score was 14.5. However, 2 patients with dementia in the placebo group had scores of 17 and 19 but did not have a delirium diagnosis according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).¹

In addition to its efficacy, ramelteon was well tolerated by acutely ill patients. In prior studies, only 3 events have been reported to occur at an incidence at least 2% higher with ramelteon (8 mg) compared with placebo: somnolence (5% for ramelteon vs 3% for placebo), dizziness (5% vs 3%), and fatigue (4% vs 2%).²⁸ No adverse events potentially attributable to the study drug were observed in our study. Lack of abuse liability has also been reported,³⁴ so ramelteon can be used safely even for delirium prevention.

Our study has several strengths, including the randomized and placebo-controlled design. The 2 groups were well balanced in terms of known delirium risk factors, and the proportion of patients with delirium in the placebo group was similar to what would be expected in this patient population. Another strength was that all participants had serious medical problems that required admission, mirroring real clinical practice. Although all patients were emergency admissions, the participation rate was nevertheless high. Because eligible patients were able to take medicine orally, their consciousness was not impaired. Many patients might thus have understood the significance of this study and been willing to participate in a placebo-controlled trial despite serious medical problems. Another explanation for the high participation rate may be that this study was rater blinded but not double blinded. Absence of support from pharmaceutical companies was another characteristic of our study.

One limitation of our study was the relatively small sample size, although the number of participants was above

Figure 3. Time to Development of Delirium



The 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 ($\chi^2 = 9.83$; $P = .002$).

the required number set by power analysis. Because of overfitting in the logistic regression analysis, a larger sample would be needed to perform more extensive multivariate analyses. Another limitation was the single-blind design. However, physicians and patients may not have had expectations about the occurrence of delirium, in which case the choice of a double-blind or rater-blind design would not have influenced the primary outcomes of delirium occurrence. Nevertheless, the lack of double blinding may bias results in favor of the active treatment.

Conclusions

To our knowledge, our study is the first to investigate the preventive effects of ramelteon on delirium. Ramelteon was associated with lower risk of delirium, even after controlling for risk factors. 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. More studies performed in real clinical practice with minimal bias are required to help physicians make rational decisions about delirium prevention.

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Author Affiliations: Department of Psychiatry, Juntendo University Nerima Hospital, Tokyo, Japan (Hatta, Usui); Department of Psychiatry, Nippon Medical School Musashikosugi Hospital, Kawasaki, Japan (Kishi); Department of Psychiatry, Hiroshima City Hospital, Hiroshima, Japan (Wada); Department of Psychiatry, Tokyo Medical and

Dental University, Tokyo, Japan (Takeuchi); Psychiatric Center Yokohama City University Medical Center, Yokohama, Japan (Odawara); Department of Environmental and Preventive Medicine, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan (Nakamura).

Author Contributions: Dr Hatta had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition of data: All authors.

Analysis and interpretation of data: Hatta, Wada, Takeuchi, Odawara, Usui, Nakamura.

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Critical revision of the manuscript for important intellectual content: Hatta, Wada, Takeuchi, Odawara, Usui, Nakamura.

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REFERENCES

- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
- Bucht G, Gustafson Y, Sandberg O. Epidemiology of delirium. *Dement Geriatr Cogn Disord*. 1999;10(5):315-318.
- Elie M, Rousseau F, Cole M, Primeau F, McCusker J, Bellavance F. Prevalence and detection of delirium in elderly emergency department patients. *CMAJ*. 2000;163(8):977-981.
- Inouye SK. Delirium in older persons. *N Engl J Med*. 2006;354(11):1157-1165.
- Michaud L, Büla C, Berney A, et al; Delirium Guidelines Development Group. Delirium: guidelines for general hospitals. *J Psychosom Res*. 2007;62(3):371-383.
- Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc*. 2001;49(5):516-522.
- Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev*. 2007;(2):CD005563.
- Liptzin B, Laki A, Garb JL, Fingerth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry*. 2005;13(12):1100-1106.
- Sampson EL, Raven PR, Ndhlovu PN, 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(4):343-349.
- Diaz V, Rodriguez J, Barrientos P, et al. Use of citicoline in the prevention of delirium in hip fracture surgery in elderly: a randomized controlled trial [in Spanish]. *Rev Neurol*. 2001;33(8):716-719.
- Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc*. 2005;53(10):1658-1666.
- Prakanrattana U, Praipatrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesth Intensive Care*. 2007;35(5):714-719.
- Larsen KA, Kelly SE, Stern TA, et al. Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. *Psychosomatics*. 2010;51(5):409-418.
- 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(7):687-694.
- Kimura R, Mori K, Kumazaki H, Yanagida M, Taguchi S, Matsunaga H. Treatment of delirium with ramelteon: initial experience in three patients. *Gen Hosp Psychiatry*. 2011;33(4):407-409.
- Ohta T, Murao K, Miyake K, Takemoto K. Melatonin receptor agonists for treating delirium in elderly patients with acute stroke. *J Stroke Cerebrovasc Dis*. 2013;22(7):1107-1110.
- Furuya M, Miyaoka T, Yasuda H, et al. Marked improvement in delirium with ramelteon: five case reports. *Psychogeriatrics*. 2012;12(4):259-262.
- Okamoto Y, Matsuoka Y, Sasaki T, Jiitsuiki H, Horiguchi J, Yamawaki S. Trazodone in the treatment of delirium. *J Clin Psychopharmacol*. 1999;19(3):280-282.
- American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616-631.
- Kubo N, Shirakawa O, Kuno T, Tanaka C. Antimuscarinic effects of antihistamines: quantitative evaluation by receptor-binding assay. *Jpn J Pharmacol*. 1987;43(3):277-282.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829.
- 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.
- Falkson G, Von Hoff D, Klaassen D, et al. A phase II study of neocarzinostatin (NSC 157365) in malignant hepatoma: an Eastern Cooperative Oncology Group pilot study. *Cancer Chemother Pharmacol*. 1980;4(1):33-36.
- Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140:566-572.
- Trzepacz PT. The Delirium Rating Scale: its use in consultation-liaison research. *Psychosomatics*. 1999;40(3):193-204.
- Kato M, Kishi Y, Okuyama T, Trzepacz PT, Hosaka T. Japanese version of the Delirium Rating Scale, Revised-98 (DRS-R98-J): reliability and validity. *Psychosomatics*. 2010;51(5):425-431.
- Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.
- Miyamoto M. Pharmacology of ramelteon, a selective MT₁/MT₂ receptor agonist: a novel therapeutic drug for sleep disorders. *CNS Neurosci Ther*. 2009;15(1):32-51.
- Liu C, Weaver DR, Jin X, et al. Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron*. 1997;19(1):91-102.
- Gerdin MJ, Masana MI, Rivera-Bermúdez MA, et al. Melatonin desensitizes endogenous MT₂ melatonin receptors in the rat suprachiasmatic nucleus: relevance for defining the periods of sensitivity of the mammalian circadian clock to melatonin. *FASEB J*. 2004;18(14):1646-1656.
- Srinivasan V, Pandi-Perumal SR, Cardinali DP, Poeggeler B, Hardeland R. Melatonin in Alzheimer's disease and other neurodegenerative disorders. *Behav Brain Funct*. 2006;2:15. doi:10.1186/1744-9081-2-15.
- 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;23(5):1005-1014.
- Bélanger L, Vallières A, Ivers H, Moreau V, Lavigne G, Morin CM. Meta-analysis of sleep changes in control groups of insomnia treatment trials. *J Sleep Res*. 2007;16(1):77-84.
- Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. *Arch Gen Psychiatry*. 2006;63(10):1149-1157.



特集

総合病院精神医学の新しい展開

Recent development of general hospital psychiatry

総合病院における高齢者支援

小田原 俊成*

Key Words 認知症 (dementia), せん妄 (delirium), 身体合併症 (physical complication), 医学教育 (medical education), 権利擁護 (elderly advocacy)

抄録：高齢者の治療は身体的問題に加えて心理社会的要因が病状に関連することから、保健医療福祉一体となった包括的支援が必要となる。本稿では、総合病院の高齢者支援における精神科医の役割について、①認知症の身体合併症治療と全人的理解、②せん妄への対応、③高齢者医学教育、④人権擁護と治療同意能力の観点から解説した。

はじめに

わが国では老年人口の急速な増加を背景に、医療機関を受療する高齢者数は増加の一途を辿っている。高齢者は完治しにくい疾患の併存や寝たきりになりやすい身体的問題とともに、種々の喪失体験(近親者との死別、社会的役割の減少)や住環境(単独および夫婦のみ高齢者世帯の増加)、経済状況といった種々の心理社会的要因が病状に密接に関連することから、保健医療福祉一体となった包括的支援が必要である。

本稿では、総合病院の高齢者支援における精神科の役割と今後の展望について述べてみたい。がん医療(サイコオンコロジー)については別稿を参照されたい。

認知症診療

1. 認知症診療実態調査

2012年3月、日本総合病院精神医学会会員向けに2011年における認知症診療に関するアンケート調査を実施し、87施設(総合病院52、大学病院24、精神科病院8、精神科診療所3)から回答を得た²⁾。このうち、認知症疾患医療センターを有するのは10施設で、内訳は総合病院4、大学病院3、精神科病院3であった。総合病院・大学病院における高齢(65歳以上)入院患者の他科併診症例のうち、認知症高齢者の割合はそれぞれ42.6%、43.3%であった(回答が不完全であった施設は除くため総合病院20施設、大学病院15施設)。一方、外来診療では年間外来新患者数全体に占める65歳以上高齢者割合は総合病院48.6%、大学病院35.2%であり、そのうち認知症高齢者の割合は、それぞれ21.6%、11.7%であった(表1)。以上の結果をまとめると、ア

Elderly supports in general hospitals

* ODAWARA Toshinari 横浜市立大学附属市民総合医療センター精神医療センター [〒232-0024 神奈川県横浜市南区浦舟町4-57]

表1 認知症診療実態調査アンケート結果（外来，併診例は除く）

	大学病院 (N=15)	総合病院 (N=20)
年間外来新患者数	952.0±539.0	375.7±246.7
高齢者数 (65歳以上)	335.4±197.1	182.7±158.6
高齢者割合 (%)	35.2	48.6
認知症高齢者数	111.0±115.4	81.0±103.7
認知症割合 (%)	11.7	21.6

高齢者割合：高齢者数 / 年間外来新患者数

認知症割合：認知症高齢者数 / 年間外来新患者数（文献2より抜粋）

アンケートに協力いただいた総合病院・大学病院精神科の新患外来患者数の約1/3～1/2が高齢者であり，他科併診高齢患者では4割強が認知症であった。また，認知症診療に関する業務内容として，鑑別診断・BPSD（認知症の行動心理症状）への対応・専門相談が大半を占めており，総合病院・大学病院ではそれに加え，BPSDが併存する患者の身体疾患への対応があげられていた。限られた施設のデータではあるが，わが国の総合病院精神科医療の現場において高齢者診療が日常的に行われている現状と，総合病院の高齢者医療における精神科の重要な役割の1つに認知症への対応（鑑別診断およびBPSD・身体疾患併存例の対応）があることを示す貴重な資料と筆者は考えている。

また，近年ではがんでだけでなく，患者の生活の質の向上を目的として認知症を緩和ケアの対象とする取り組みが海外で始まっている。朝生は，総合病院において認知症患者の疼痛管理が適切に行われていない現状を指摘し，認知症に伴う精神的苦痛への対応とともに，今後わが国においても重要な課題になると指摘している⁴⁾。身体的治療とともに，心理社会的存在として認知症患者の理解を深め，生活の質に焦点をあてた支援・ケアの提供を多職種協働で行うという一連のプロセスの統括者として，総合病院精神科医の果たすべき役割は今後さらに重要になると思われる。

2. 救急医療

救急医療機関を受診する高齢者は増加しており，全国の救急病院受診者の約半数が高齢者で

あることが指摘されている。久保田らは，仙台市立病院の救命救急センター外来（1～3次救急）を2007年3月1カ月間に受療した65歳以上高齢者を認知症（およびその疑い）群88例と非認知症群219例に分け，両群の臨床的特徴を比較した³⁾。その結果，前者では身体的重症度が高く死亡の転帰をとる割合が高い一方で社会的入院の割合も高く，そうした症例では外来診察時間も長かったことを報告している。認知症患者がこうした臨床的特徴を示す理由として，事故，服薬コンプライアンス低下による併存疾患の悪化や身体機能の低下，症状の自発的表出の困難さにより対応が遅れやすいことなどが推察される。救急搬送困難事例として認知症患者が少くないことは，こうした対応困難性が原因と考えられる。疾病教育や心理社会的背景をふまえた生活面のアドバイスは，救急受診の繰り返しを防止するうえで，救急の現場においても精神科医の重要な支援業務となっていく可能性がある。

3. 入院治療

認知症高齢者は入院においてもさまざまな治療上の困難を伴う。自施設の精神病床（精神科病棟）に入院した65歳以上高齢者を認知症群（身体合併症併存例）106例と非認知症群213例の2群に分類し，入院処遇について比較したデータを表2に示す。認知症群では非自発入院，行動制限（隔離，身体拘束）の割合が高かった。この結果から，認知症入院患者の入院同意能力は他の精神疾患と比較してもさらに不十分であること，治療に対する協力が十分に得られにく

表2 精神医療センター高齢入院患者症例における認知症群の臨床的特徴

	認知症群 (106例)	非認知症群 (213例)
平均年齢	74.6±6.8歳*	71.7±6.1歳
在院日数	48.9±29.8日	63.2±35.4日*
非自発入院 (%)	75.1*	57.3
隔離 (%)	44.0*	24.3
拘束 (%)	37.2*	16.4
自宅退院 (%)	24.7	60.3*

認知症群は非自発入院、行動制限を要する割合が高かった。また、入所・転院の割合が高く、自宅退院率が低かった。* $p < 0.05$

い傾向がみてとれる。また、認知症群の在院日数は非認知症群と比べて短かく(施設入所や転院が多いため)、自宅退院率は低かった。以上の結果は、認知症患者の一般病棟における対応困難性と身体疾患を有する認知症患者の在宅治療および介護の困難さの一端を示唆する所見と考えられる。さらに、認知症患者は入院中新たに判明または発症する身体合併症にも注意が必要である。2011～2012年に精神科病棟に身体治療目的で入院した認知症患者54人中、約2割にあたる11人に身体疾患が併発した。呼吸器・尿路感染症や転倒による骨折を抜いて、深部静脈血栓症(DVT)が最も多く、5人に認められた。認知症患者は高齢、向精神薬使用、身体疾患の併存のほか、身体拘束を用いる頻度が高く、全例がDVTの高リスク群に該当していた。さらに、(精神科2次・3次)救急入院症例ほど、BPSDの背景にある身体疾患の評価・治療が十分に行われておらず、環境調整を含めた複合的な対応を要する事例が多かった。

わが国の認知症施策推進5か年計画(オレンジプラン)の原案となった地域精神保健医療体制の構築に向けた検討チーム(第2R, 認知症と精神医療)とりまとめ案では、重度のBPSDと身体合併症を併存する認知症患者の入院医療について、合併症の状態像に応じた(精神)病床の受け入れ先の選別(総合病院精神科と精神科病院の役割分担)が推奨されている。すなわち、身体疾患急性期の治療は有床総合病院精神科で行い、慢性疾患の治療は精神科病院が担うとい

うものである。しかし、急性期身体疾患の入院対応が可能な認知症疾患医療センターを有する総合病院の病床整備は十分に進んでおらず、また、総合病院であっても精神科で対応可能な身体疾患は限られており、身体疾患の種類および重症度により認知症患者の受け入れ先探しに難渋するケースは少なくない。2008年の医療施設調査では総合病院精神科のない二次医療圏が全国に1/3あることが報告され、その後診療報酬の誘導効果により無床精神科を有する総合病院数はこの年を境に増加に転じている。今後、精神科医およびリエゾンチームには、一般病床での認知症患者の受け入れ促進の役割が期待されよう。

高橋は、総合病院精神科が地域医療の中心となりうる前提として、1)精神科病棟で身体的な問題が発生した場合でも簡便に身体科へ相談できること、2)精神的トリアージの役割をすること、3)他の社会資源と協働することをあげている⁵⁾。地域の認知症包括ケアにおいて、総合病院精神科は欠かすことのできないワンピースといえる。

● 高齢者コンサルテーション

筆者の所属施設は救命救急センターをはじめとして10の疾患別センターおよび19の診療科からなる急性期治療を特徴とした726床の大学附属病院である。2012年1年間に救命救急センターを除く他診療科入院患者に対する併診症例290例中、60歳以上(高齢群)は191例(65.9%)

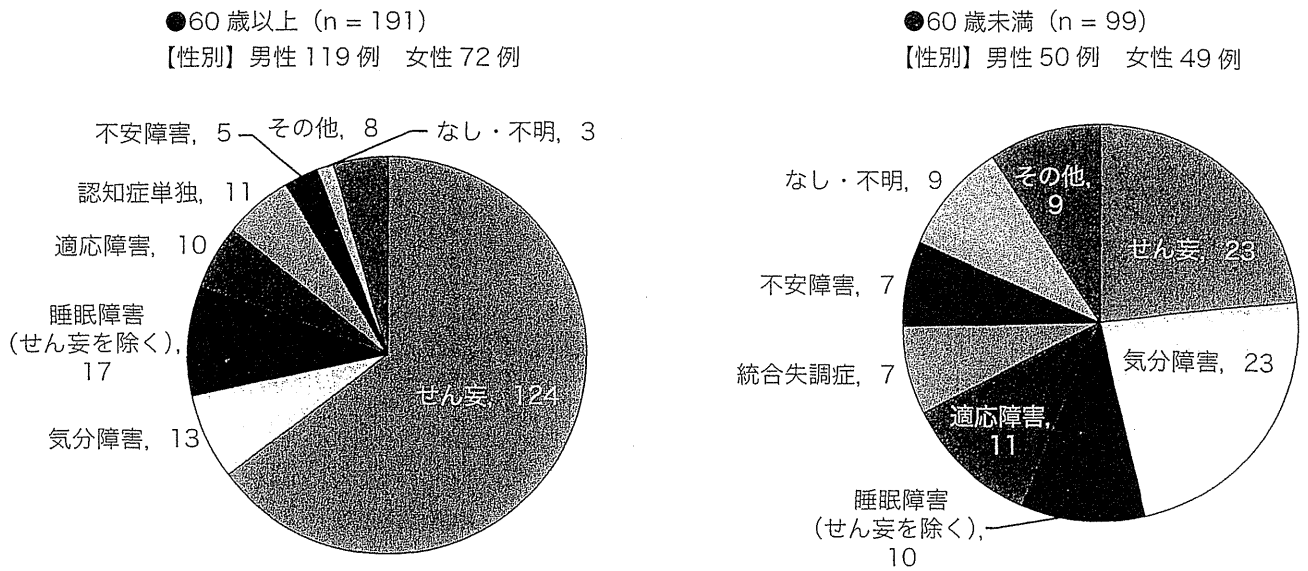


図1 2012年精神医療センター他科併診入院患者（救命センター除く）診断内訳

であった(図1)。併診の対象となった症状および主病名の内訳は、高齢群でせん妄が124例(認知症合併例含む, 64.9%)と最も多く約2/3を占め、以下睡眠障害、気分障害、認知症(せん妄を伴わない)、適応障害、不安障害と続いた。60歳未満(99例)の診断内訳(せん妄23.2%、気分障害23.2%、適応障害11.1%、睡眠障害10.1%、統合失調症7.1%、不安障害7.1%)と比較すると、高齢群でせん妄の占める割合が大きく増加していた。当院のみのデータではあるが、総合病院では高齢者に対する精神科医の役割として、せん妄対応が重要であることを示している。最近、Hattaらは、わが国の常勤精神科医を有する総合病院で行ったせん妄患者の多施設共同観察研究において、抗精神病薬が投与された2千数百例(平均年齢73.5歳)中、重篤な有害事象を呈した症例は1%に満たず、1週間以内に半数以上でせん妄が改善したことを報告している¹⁾。高齢者に対する抗精神病薬投与の危険性が指摘されて久しいが、総合病院精神科のvalueとして大いにアピールされるべきであろう。今後、総合病院の高齢せん妄患者に対し、リエゾンチームによる非薬物療法的アプローチを含む包括的対応の治療効果が期待される。

高齢者医学教育における総合病院精神科の役割

2007年、米国医科大学連合は医学生が卒業後適切な高齢者診療を行うために必要な最低限の到達目標(minimum geriatric competencies)を設定した。全8分野中、認知行動障害と緩和ケア、入院ケアの3つの分野において精神医学的知識の必要性が取り上げられている。すなわち、認知行動障害の分野では、せん妄、認知症、うつ病の臨床的特徴の理解と鑑別、せん妄の原因検索、記憶障害を有する高齢者の認知機能評価の実践、せん妄・認知症患者に対する非薬物療法の立案を、緩和ケアの分野では、心理・社会・スピリチュアルな領域でのニーズの確認とチーム医療への誘導について、入院ケアの分野では、身体・薬物的拘束の適応と禁忌が記載されている。これらは専門性を問わず知っておくべき知識とされ、高齢者診療における精神医学的アプローチの重要性がみてとれる。先に自施設の高齢者コンサルテーション症例の内訳で示したように、こうした病態の鑑別および治療を実践できるのは総合病院であることは改めて強調するまでもないであろう。また、入院ケア分野に記載されたりエゾンチームによる多職種が連携

した退院支援も精神科が主導すべき役割といえる。

● 高齢者の権利擁護と治療同意能力

近年、高齢者虐待防止法の施行により(認知症)高齢者に対する人権擁護の意識が高まりつつある。児童虐待に比べると、病院内における高齢者虐待例に対する認知度はいまだ低い状況にあるが、当院では救命救急センターを含む一般病棟に入院する高齢患者に虐待事例が散見され、徐々に対応件数が増えつつある。虐待が疑われる事例に対しては、随時患者人権擁護委員会を開催し、主治医、精神科医、他科医師、看護師、ケースワーカー、行政職、地域支援事業者などによる多職種ミーティングを開催し対応を検討している。特に身体的虐待事例は総合病院で対応する機会が多く、高齢者虐待に対するe-learningを用いた全職員研修を毎年行っている。

認知症患者で非自発入院が多いことは先に述べたが、個別の医行為に対する同意能力の判定も総合病院では重要な問題となっている。高齢者に限定されるものではないが、認知症のように認知機能障害が漸次進行する疾患では治療による同意能力の回復は必ずしも期待できないため、身体侵襲性の高い検査や治療を行う場合にしばしば問題が生じる。通常、わが国では家族が代理同意を行うことが多いが、いまだ医療同意代行に関する法律は制定されていない。単身者の場合や本人・家族間、家族内、家族・後見人間の意見が不一致の場合など、治療方針が定まらないケースが散見される。このような症例はしばしば院内の臨床倫理審査委員会で治療方

針が検討されるが、多くの場合精神疾患が関与するため、精神科医が同意能力に関する意見を具申することになる。最近では、精神科医が治療同意能力の評価尺度を利用して認知症患者に治療法の理解と選択を援助する試みを行う施設も出てきている。今後、総合病院精神科には、高齢患者の人権擁護、治療方針に関する意見調整役としての役割も期待されよう。

● おわりに

総合病院の高齢者支援における精神科医の重要な役割として、①認知症の身体合併症治療と全人的理解、②せん妄への対応、③高齢者医学教育、④人権擁護と治療同意能力の観点から解説した。

当院の併診患者統計をまとめていただいた精神医療センター日野耕介先生に感謝申し上げます。

文献

- 1) Hatta K, Kishi Y, Wada K et al : Antipsychotics for delirium in the general hospital setting in consecutive 2453 inpatients : a prospective observational study. *Int J Geriatr Psychiatry* 29 : 253-262, 2014
- 2) 近藤大三, 小田原俊成, 粟田主一ほか : 日本総合病院精神医学会会員に対する認知症診療に関するアンケート調査. *総合病院精神医学* 25 : 171-177, 2013
- 3) 久保田洋介, 亀山元信, 村田祐二ほか : 救命救急センターにおける認知症高齢者の救急医療. *老年精神医学雑誌* 18 : 1204-1209, 2007
- 4) 小川朝生 : 精神科医療と緩和ケア. *精神医学* 56 : 113-122, 2014
- 5) 高橋武久 : 地域精神医療における総合病院の役割. *総合病院精神科は地域において何をなすべきか*. *精神神経学会誌* 105 : 601-608, 2003

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夕暮れ症候群とせん妄

小田原 俊 成

1. はじめに

夕暮れ症候群とは、夕方から夜にかけて精神行動症状が出現または増加する現象に用いられる表現であり、精神医学的診断や専門用語でないにもかかわらず世界的に広く使用されている。特に、認知機能障害を有する高齢者あるいは施設入所高齢者を対象とした報告が多い。症状の厳密な定義はないが、一般的には混乱、失見当識、不安、焦燥、幻覚妄想、攻撃性、徘徊、抵抗、叫声などの症状がとりあげられている (Khachiyants et al., 2011)。一方、せん妄とは注意と認識の障害であり、(認知症や重篤な意識障害では説明できない) 短期間に変動する認知機能障害として定義される精神医学的診断名である。2013年に発表されたDSM5診断基準では、せん妄の診断に長らく使用されていた意識の障害という診断要件が認識の障害へと変更になった (American Psychiatric Association, 2013)。臨床的に診断困難であった軽度の意識障害を除外して神経認知ドメインの障害の有無で評価を行う手法の導入は、診断の評

価者間信頼性を高める上で重要な変更点と思われる。夕暮れ症候群とせん妄にみられる精神行動症状の中で幻覚妄想に特有の病態機序は明らかとなっていないため、本稿ではこれら症候群全体に共通する原因および病態機序について概説する。

2. 夕暮れ症候群

夕暮れ症候群の出現頻度に関する報告は調査対象や居住環境により差がみられるが、アルツハイマー型認知症 (Alzheimer's disease; AD) の2.4~25%に出現することが報告されている (Alzheimer's Association, 2006)。一般に、認知機能障害が重度になるほど出現頻度が高い (Volicer et al., 2001) とされるが、認知症の種類や性別による差は明らかでない。夕暮れ症候群の発症機序は不明だが、生理学的要因、心理・環境要因の関与が推定されている。以下にこれまで報告されている夕暮れ症候群を来す原因と、推定される病態機序について解説する。

1) 感覚遮断

夕暮れ症候群の原因として、これまでに日中の照度光不足との関連を指摘する観察研究が多数報告され、光療法や環境光の調整が夕暮れ症候群の管理として用いられてきた (Ancoli-Israel et al., 2003)。この考え方は概日リズム障害の研究へとつながっている。

Sundowning and delirium

Toshinari Odawara

横浜市立大学附属市民総合医療センター精神医療センター

[〒232-0024 横浜市中区浦舟町4-57]

Psychiatric Center, Yokohama City University Medical Center (4-57

Urafune-cho, Minami-ku, Yokohama, Kanagawa-ken 232-0024)