INTRODUCTION

Drug-induced hyponatremia can be caused by diuretics that reduce the ability to dilute urine and other drugs that affect vasopressin (AVP). These drugs are thought to affect AVP through mechanisms such as increased AVP secretion in the hypothalamus, enhanced AVP action in the kidney, and decreased AVP secretion threshold of osmotic receptors. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a condition in which water reabsorption is overstimulated by AVP and water diuretic deficiency occurs despite hyponatremia. Most drug-induced SIADH is due to antidepressants such as citalopram, venlafaxine, and escitalopram. In addition, the use of citalopram, escitalopram, mirtazapine, paroxetine, and sertraline increase the risk of hospitalization due to hyponatremia. On the other hand, the exact frequency of SIADH as a side effect of duloxetine is unknown because this has been reported only in spontaneous reports. Duloxetine was formally studied in just one prospective observational surveillance study, which found an incidence rate of 0.11% (95% CI 0.044–0.626), although the duloxetine group was quite small (1%) owing to the low frequency of duloxetine prescription in their study population.

We encountered by chance two cases of hospitalization due to SIADH without any symptoms after initiating duloxetine treatment due to pain.
We present a case involving an 83-year-old Japanese male who suffered from hyponatremia without any symptoms. Four years earlier, he complained of numbness and pain in both lower limbs, whose cause was unknown. Duloxetine 20 mg was prescribed by the Department of Orthopedics. Pain did not improve, and anxiety, irritation, insomnia, and loss of appetite appeared. He was referred to the Department of Diagnostic and Generalist Medicine, which also prescribed duloxetine 20 mg/day. A blood test at a regular visit revealed hyponatremia (110 mmol/L) 35 days after initiating the duloxetine 20 mg/day. On the same day, he was urgently admitted to the Department of Diagnostic and Generalist Medicine. Laboratory data revealed Na 110 mmol/L, K 5.2 mmol/L, Cl 77 mmol/L, creatine 0.67 mg/dL, blood urea nitrogen 15.0 mg/dL, aspartate aminotransferase 30 U/L, alanine aminotransferase 37 U/L, white blood cell 5.9 × 10^9/L, red blood cell 5.32 × 10^{12}/L, hemoglobin 15.4 g/dL, adrenocorticotropic hormone 26.8 pg/mL, cortisol 21.36 μg/mL, thyroxine 0.93 ng/dL, and thyroid-stimulating hormone 1.08 μIU/mL. Estimated serum osmolality was 232 mOsm/kg. Serum vasopressin concentration was 2.2 pg/mL. Hypertonic urine: estimated urine osmolality 385 mOsm/kg, urine sodium concentration 55 mmol/L. We started sodium correction by intravenous drip (5–10 mEq/day). Because his depression worsened and he began to express suicidal ideation, he was referred to the Department of Psychiatry on day 4 of admission. Based on the course of treatment, the patient was diagnosed with suspected drug-induced SIADH. Therefore, the duloxetine 20 mg was discontinued and replaced with mirtazapine 15 mg/day. Due to daytime sleepiness, his prescription was changed from mirtazapine 15 mg/day to sertraline 50 mg/day on day 15 of admission. The serum sodium concentration increased gradually after he discontinued duloxetine (Figure 1).

Medications other than pain medications, alcohol history, urine drug screen, smoking history, and chest X-ray revealed no cause for SIADH. His depression ameliorated after he started sertraline. During hospitalization, searches for central nervous system disorders, malignancy, other medications, pulmonary disease, hormone deficiency, hypopituitarism, and hypothyroidism, etc., did not reveal any abnormalities.

We present a case involving a 71-year-old Japanese female who suffered from hyponatremia and depression. Three years earlier, she complained of back and buttock pain, was tentatively diagnosed by an orthopedic surgeon as having piriformis syndrome and was treated with intramuscular injections of painkillers. Although duloxetine 20 mg/day, pregabalin 150 mg/day and celecoxib 100 mg/day were prescribed for 1 month, her pain did not improve, and anxiety, irritation, insomnia, and loss of appetite appeared. The patient went to the emergency room of our hospital for suicide attempts by wrist and neck cutting spurred by the lack of improvement in her pain. A blood test at the time revealed hyponatremia (108 mmol/L) 40 days after initiating duloxetine 20 mg/day. On the same day, she was urgently admitted to the Department of Diagnostic and Generalist Medicine. Laboratory data revealed Na 108 mmol/L, K 5.2 mmol/L, Cl 73 mmol/L, creatine 0.36 mg/dL, blood urea nitrogen 10 mg/dL, aspartate aminotransferase 30 U/L, alanine aminotransferase 37 U/L, white blood cell 5.9 × 10^9/L, red blood cell 4.3 × 10^{12}/L, hemoglobin 13.6 g/dL, adrenocorticotropic hormone 10.7 pg/mL, cortisol 22.0 μg/mL, thyroxine 0.93 ng/dL, and thyroid-stimulating hormone 1.08 μIU/mL. Serum osmolality was 223 mOsm/kg. Serum vasopressin concentration was 0.4 pg/mL. Hypertonic urine: urine osmolality 361 mOsm/kg, urine sodium concentration 34 mmol/L. Her depressive mood worsened, and she was admitted to the psychiatric department on the same day due to suicide attempts. Duloxetine was increased from 20 mg/day to 40 mg/day because of the deterioration of depression. Although we started sodium correction by intravenous drip (5–10 mEq/day), the sodium level did not exceed 130 mmol/L. Based on the course of treatment, the patient was diagnosed with suspected duloxetine-induced SIADH. Her prescription was changed to mianserin 15 mg/day on day 15. Serum sodium increased to 140 mmol/L soon after discontinuation of duloxetine. His depression was ameliorated after starting mianserin 60 mg/day, and she was discharged on day 62. In the present case, there was no evidence of SIADH in medications other than pain treatment, alcohol history, urinary drug screen, smoking history, or chest X-ray. In this case, too, during the hospitalization, the investigators searched for central nervous system disorders, malignancy, other drugs, pulmonary disease, hormone deficiency, hypopituitarism and hypothyroidism, but found no abnormality.
4 | DISCUSSION

These are two patients who developed asymptomatic SIADH after duloxetine administration and recovered after duloxetine discontinuation. Although many pathologic conditions may be associated with hyponatremia, no physical disease causing SIADH was found in these cases. Therefore, based on the clinical course of these cases, we concluded that SIADH was induced by duloxetine administered for low back pain.

Elderly people tend to be more prone to hyponatremia and also to induce SIADH. Hyponatremia is associated with specific risk factors, such as older age and diuretic use, and our patients were both older, but they did not take diuretics. The ability of the kidneys to concentrate and dilute urine decreases in old age, as does the ability to retain sodium, resulting in increased basal secretion of AVP. In addition, SIADH is likely to occur because it tends to react excessively to osmotic stimulation. The mechanism by which SIADH is caused by antidepressants is thought to be an AVP-enhancing effect, enhanced AVP action in the renal collecting duct, and impaired AVP secretion-suppressing pathway. It is possible that tricyclic antidepressants are involved in AVP secretion via the central nervous system, which stimulates thirst by anticholinergic action, but the detailed mechanism is unknown. There has been no direct verification that antidepressant-induced SIADH is more common in the elderly than in the young. However, taking into account the respective effects of age and antidepressants on AVP, it may be said that SIADH due to antidepressant use in the elderly is more likely to occur than in the young.

There are 8 case reports regarding SIADH associated with duloxetine due to pain. The average (range) age and daily dose have been 75.3 years (68–80 years) and 38.8 mg (20–60 mg), respectively, which are similar to our data. However, the average (range) dosage period has been 3.6 days (1–12 days), and the dosage periods of our cases were 35 days and 40 days, respectively. This is the first report suggesting that it takes a long time for duloxetine to induce SIADH. This may be because depression secondary to pain masks SIADH-related symptoms, resulting in asymptomatic SIADH and delayed detection. In fact, different case reports have found that it took 5 weeks to 3 years for SIADH to arise in patients with depression who took duloxetine. To date, it is unclear how duloxetine-induced SIADH differs between depression and pain disorders. It will become clearer as more cases are accumulated.

AUTHOR CONTRIBUTIONS
RM, MS, YO, and MR were involved in the clinical investigations. NYF wrote the manuscript. TS, NYF, and KS were involved in the literature review. All authors read and approved the final manuscript.

CONFLICT OF INTEREST
Authors declare that they have no competing interests to report.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEW BOARD
The ethics committee of the School of Medicine at Dokkyo Medical University determined that there was no need to review this case.

INFORMED CONSENT
Written informed consent was obtained from the parents for the publication of this case reports.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL
Not available.

ANIMAL STUDIES
Not available.

ORCID
Norio Yasui-Furukori https://orcid.org/0000-0002-4414-3770

REFERENCES
1. Vantyghem MC, Balavoine AS, Wémeau JL, Douillard C. Hyponatremia and antidiuresis syndrome. Ann Endocrinol (Paris). 2011;72(6):500–12.
2. Shepshelovich D, Schechter A, Calvarysky B, Diker-Cohen T, Rozen-Zvi B, Gafter-Gvili A. Medication-induced SIADH: distribution and characterization according to medication class. Br J Clin Pharmacol. 2017;83:1801–7.
3. Gandhi S, Shariff SZ, Al-Jaishi A, Reiss JP, Mamdani MM, Hackam DG, et al. Second-generation antidepressants and hyponatremia risk: a population-based cohort study of older adults. Am J Kidney Dis. 2017;69:87–96.
4. Letmaier M, Painold A, Holl AK, Vergin H, Engel R, Konstantinidis A, et al. Hyponatraemia during psychopharmacological treatment: results of a drug surveillance programme. Int J Neuropsychopharmacol. 2012;15:739–48.
5. Peri A. Management of hyponatremia: causes, clinical aspects, differential diagnosis and treatment. Expert Rev Endocrinol Metab. 2019;14:13–21.
6. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BG. Antidepressants and the risk of hyponatremia: a class-by-class review of literature. Psychosomatics. 2014;55:536–47.
7. Safdieh JE, Rudominer R. A case of hyponatremia induced by duloxetine. J Clin Psychopharmacol. 2006;26:675–6.
8. Nakamura M, Satoh Y, Hiraoka A, Fujita Y, Nagamine T. Duloxetine-induced hyponatremia in the elderly. Clin Neuropsychopharmacol Ther. 2012;3:33–6.
9. Anwari JS, Hazazi AA. Another cause of headache after epidural injection. Neurosciences (Riyadh). 2015;20:167–9.
10. Amoako AO, Brown C, Riley T. Syndrome of inappropriate antidiuretic hormone secretion: a story of duloxetine-induced hyponatraemia. BMJ Case Rep. 2015;2015:bcr2014208037.
11. Kamei S, Kaneto H, Tanabe A, Irie S, Hirata Y, Shimoda M, et al. Rapid onset of syndrome of inappropriate antidiuretic hormone secretion induced by duloxetine in an elderly type 2 diabetic
patient with painful diabetic neuropathy. J Diabetes Investig. 2015;6:343–5.

12. Wang D, Lai J, Lu S, Huang M, Hu S, Xu Y. Rapid-onset hyponatremia and delirium following duloxetine treatment for postherpetic neuralgia: case report and literature review. Medicine (Baltimore). 2018;97:e13178.

13. Takayama A, Nagamine T, Matsumoto Y, Nakamura M. Duloxetine and angiotensin II receptor blocker combination potentially induce severe hyponatremia in an elderly woman. Intern Med. 2019;58:1791–4.

How to cite this article: Sato A, Yasui-Furukori N, Oda Y, Yang M, Suzuki Y, Shinozaki M, Asymptomatic syndrome of inappropriate secretion of antidiuretic hormone (SIADH) following duloxetine treatment for pain with depression: Two case reports. Neuropsychopharmacol Rep. 2022;42:387–390. https://doi.org/10.1002/npr2.12279