Department of Pharmacy[1], Juntendo University Hospital; Department of Clinical Pharmacy[2], Faculty of Pharmaceutical Sciences, Kobe Gakuin University; Department of Clinical Pharmacy Research and Education[3], Graduate School of Pharmaceutical Sciences, Osaka University; Department of Hospital Pharmacy[4], Nagasaki University Hospital; Department of Clinical Pharmacy[5], Kagawa School of Pharmaceutical Sciences, Tokushima Bunri University; Department of Pharmacy[6], National Hospital Organization Sendai Medical Center; Department of Education and Research Center for Pharmacy Practice[7], Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts; Department of Pharmacy[8], Nippon Medical School Tamanagayama Hospital; Research Promotion Committee[9], Japanese Society for Pharmaceutical Palliative Care and Sciences, Japan

Pharmacist interventions for adverse drug reactions in palliative care: A multicentre pilot study

E. Kose[1,#], S. Nakagawa[2,9,#,*], K. Niki[3,9], J. Hashizume[4], T. Kawazoe[5,9], N. Suzuki[6], M. Uchida[7,9], H.Takase[8,9]

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**Corresponding author: Sari Nakagawa, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, 1-1-3 Minatojima, Chuo-ku, Kobe-shi, Hyogo 650-8586, Japan*
nakagawa@pharm.kobegakuin.ac.jp
[#]These authors contributed equally to this work.

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Objectives: This study aimed to investigate adverse reactions to medications administered during palliative care and compare the responses of Board-Certified Pharmacists in Palliative Pharmacy (BCPPP) and non-BCPPP professionals. *Methods*: This multicentre prospective survey included hospital and community pharmacists who are members of the Japanese Society for Pharmaceutical Palliative Care and Sciences. Study participants included patients who experienced new drug reactions during the study period and responded to the requested survey items. The follow-up period for each eligible patient began on the day the pharmacists initiated the intervention and ended at discharge, death, or after one month of intervention. The primary endpoint was the impact of pharmacist intervention on adverse drug reactions. The pharmacists included in the study evaluated the severity of adverse drug reactions to assess the effect of their intervention using an integrated palliative care outcome scale before and after the intervention. *Key findings*: During the survey period, 79 adverse drug reaction intervention reports from 69 patients were obtained from 54 pharmacists (28 certified and 26 non-certified). The response rate was 1.62% (54/3,343). The management of palliative pharmacotherapy side effects by BCPPP and non-BCPPP significantly improved the patients' activities of daily living ($P < 0.001$). The BCPPP group intervened for significantly more patients with adverse drug reactions and overall adverse drug reactions than the non-BCPPP group ($P < 0.023$ and $P < 0.013$, respectively). *Conclusion*: BCPPP interventions can improve symptom management.

1. Introduction

The importance of palliative care in Japan is increasing annually. In April 2007, the *Cancer Control Act* clarified three areas of cancer care: prevention, treatment, and palliative care (The Japanese Ministry of Health, Labour and Welfare, Cancer Control Act 2007). Thus, palliative care was established as medical care provided simultaneously with treatment following cancer diagnosis. Therefore, palliative care teams play an increasingly important role in improving and promoting the quality of life of patients.

The role of pharmacists in palliative care is also increasing and includes supporting the appropriate use of medical narcotics and other drugs, monitoring adverse drug reactions, and ensuring the collaborative and cooperative provision of care to patients with cancer in their homes. The American Society of Health-System Pharmacists published a statement on pharmacists' contributions to hospice and palliative care highlighting their clinical, educational, administrative, and supportive roles (Herndon et al. 2016). The National Consensus Project for Quality Palliative Care clinical practice guidelines identified the importance of assembling an appropriately trained team that included pharmacists (National Consensus Project for Quality Palliative Care 4th edition). In 2007, the Japanese Society for Pharmaceutical Palliative Care and Sciences (JSPPCS) was established primarily for pharmacists providing palliative care such as pain and symptom management for cancer. Since then, pharmacists have become an important component of the palliative care team and their work has been recognised by non-pharmacist healthcare professionals. In 2010, the JSPPCS introduced the concept of Board-Certified Pharmacists in Palliative Pharmacy (BCPPP) to foster professional pharmacists who understood the essence of palliative medicine, were well-informed about palliative pharmacotherapy, and contributed to multidisciplinary patient care. The BCPPP is accredited by this society through the following training and experience: at least five years of clinical service, engagement in palliative care at a hospital or clinic with a palliative care team or ward, Opportunity to present research in the field of palliative care, opportunity to present at least 30 cases of intervention, participation in workshops approved by the society, and passing the certification examination. As of September 2021, with the number increasing annually, 739 certified pharmacists were working in multiple fields. The involvement of pharmacists in palliative care teams in various settings has been previously reported (Ma et al. 2016; Dayer et al. 2021; Demler 2016; Walker 2010: Wlison et al, 2011). In 2016, Ma et al. (2016) reported that pharmacist-led outpatient palliative care practices identified drug-related problems in the management of pain, constipation, nausea, and vomiting. Medication changes included changes in the dosage and/or initiation of a new medication. Trends in pain improvement and stabilisation were observed during subsequent clinic visits. A study conducted to identify factors influencing pharmacists' recommendations and to determine whether acceptance was a significant predictor of clinical outcomes showed that physicians' acceptance of pharmacists' recommendations, the recommending pharmacists, and the patients' proximity to death were significant predictors of achieving the desired clinical outcome (Ma et al. 2016; Dayer et al. 2021; Demler et al. 2016;

Table 1: Background of the participants

			All pharmacists n = 54		BCPPP n = 28		Non-BCPPP n = 26		P-value
			n	%	n	%	n	%	
Workplace	Community pharmacy		16	29.6	5	17.9	11	42.3	
	Hospital/clinic		38	70.4	23	82.1	15	57.7	0.074 a)
	Palliative care team	Yes	32		19		13		
		No	6		4		2		
	Palliative care hospital ward	Yes	7		4		3		
		No	31		19		12		
Acquisition of cancer-related board-certified OPS/POP		Yes	19	35.2	11	39.3	8	30.8	0.577 a)
		No	35	64.8	17	60.7	18	69.2	
Years of service median (min – max), years			15	(2–38)	16	(10–31)	13	(2–38)	0.100 b)

a) Fisher's exact probability test b) Wilcoxon's rank-sum test
Abbreviations: BCPPP, board-certified palliative pharmacist; OPS, oncology pharmacy specialist; POP, oncology pharmacist
The nominal variable was the number of participants (%), and the continuous variable was the median (range).

Table 2: Background of patients with pharmacist intervention

		Patients who received intervention from BCPPPs		Patients who received intervention from non-BCPPPs		P-value*
		n	%	n	%	
Sex	Male	20	40.0	14	73.7	0.016
	Female	30	60.0	5	26.3	
Age, y	40–49	9	18.0	1	5.3	0.690
	50–59	8	16.0	4	21.1	
	60–69	10	20.0	3	15.8	
	70–79	13	26.0	7	36.8	
	80–89	10	20.0	4	21.1	
Main disease	Mammary gland cancer	11	22.0	1	5.3	0.003
	Lung cancer	6	12.0	12	63.2	
	Liver/bile duct cancer	5	10.0	2	10.5	
	Rectal/anal cancer	5	10.0	0	0	
	Pancreatic cancer	5	10.0	0	0	
	Urinary cancer	4	8.0	1	5.3	
	Head and neck	0	0	2	10.5	
	Other	14	12.6	0	0	
	No response	0	12.7	1	5.3	

		Patients who received intervention from BCPPPs		Patients who received intervention from non-BCPPPs		P-value*
		n	%	n	%	
Disease advancement	Initial onset	16	32.0	8	42.1	0.628
	Metastasis	22	44.0	5	26.3	
Place of medical treatment (duplicates present)	Recurrence	9	18.0	5	26.3	
	Recurrence and metastasis	2	4.0	1	5.3	
	Other	1	2.0	0	0	
	General hospital ward	25	49.0	16	84.2	0.013
	Patient's home	22	43.1	2	10.5	0.011
	Palliative care hospital ward	2	3.9	1	5.2	1
	Chemotherapy room	1	2.0	0	0	1
	Outpatient	1	2.0	0	0	1
Purpose of admittance /hospital visit (duplicates present)	Chemotherapy	31	55.6	6	26.1	0.032
	Radiotherapy	6	10.8	3	13.0	0.670
	Home medical care	3	5.6	0	0	0.056
	Tests	2	3.6	1	4.3	1
	Pain control	1	1.1	1	4.3	0.478
	Chemoradiotherapy	0	0	1	4.3	0.276
	No treatment (including BSC)	13	23.2	11	47.8	0.023

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy; BSC, best supportive care

Walker et al. 2010; Wilson et al. 2011). As evident from the above, the intervention of pharmacists in palliative care can contribute to pain control and early detection of drug reactions in patients.
In Japan, although the outcomes of palliative care team activities by pharmacists have been evaluated (Nakagawa et al. 2019), no outcome studies have been conducted on the activities of BCPPP professionals or the extent of their contribution to palliative pharmacotherapy. Therefore, this study aimed to determine the responses of BCPPP and non-BCPPP professionals to potential adverse drug reactions using a survey to investigate the importance of board certification for decision-making in cases of adverse drug reactions.

2. Investigations and Results

2.1. Response rate and participation background

Of the 3,343 pharmacists who were members of the JSPPCS, 109 participated in the survey. However, among the pharmacists who indicated a willingness to contribute, those who did not provide background information such as their workspace, acquisition of cancer-related and board-certified OPS/POP, and years of service were excluded, and a total of 54 were included. The response rate was 1.62% (54/3343). The participants' backgrounds are summarised in Table 1. No significant differences were observed between the two pharmacist groups in any category.

2.2. Differences in the frequency of intervention between BCPPP and non-BCPPP

The number of daily workplace interventions per week was also assessed. Overall, in hospitals, the most frequent interventions were once a week: 23.7% (9/38) in general wards, 42.9% (3/7) in palliative care units, and 34.4% (11/32) in palliative care teams; less than once a week in community pharmacies; and 2–4 times/day at home, with the exception of outpatient services. No statistically significant differences were observed in the frequency of intervention between the two groups. One of the most interesting findings was that only 7.7% (1/13) of the non-BCPPP interventions were performed more than five times a week by the palliative care team, whereas those by the certified pharmacists constituted 31.6% (6/19) (Supplemental Material S1).

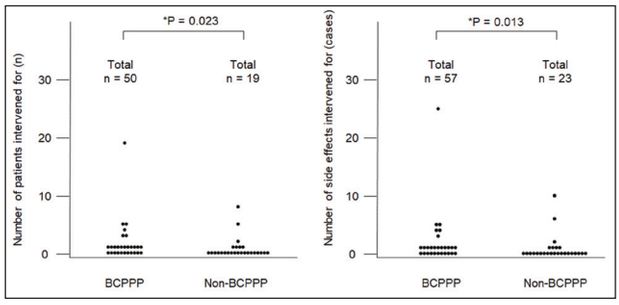

Fig. 1: Number of interventions for adverse drug reactions by pharmacists . *Wilcoxon's rank-sum test. Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

2.3. Background of patients under intervention

Table 2 summarises the background of the patients treated in this study. The group that received interventions from BCPPP underwent a significantly higher number of interventions for cancer chemotherapy (P = 0.032) and at home (P = 0.011). The group that received interventions from non-BCPPPs included a significantly higher number of men (P = 0.016). Lung cancer was the most common cancer type in this group (63.2%; 12/19). It was also characterised by more interventions for patients receiving best supportive care (BSC) (P = 0.023).

2.4. Status of interventions for adverse events

Figure 1 shows the total number of patients treated by pharmacists, number of interventions, and number of adverse drug reactions. In terms of the total number of interventions in patients, the BCPPP group (n = 28) performed 57 interventions in 50 patients, whereas the non-BCPPP group (n = 26) performed 22 interventions in 19 patients. The BCPPP group had significantly more intervention patients (P = 0.023) and interventions (P = 0.013) than the non-BCPPP group. Constipation (BCPPP vs. non-BCPPP: 26.3% vs. 36.4%), nausea or vomiting (10.5% vs. 9.1%), somnolence (10.5% vs. 22.7%), and other symptoms (52.6% vs. 31.8%) were the adverse reactions that the participating pharmacists described. No significant differences were observed between the two pharmacist groups for any symptoms. However, 'other symptoms' accounted for 52.6% (30/57) of the symptoms in the BCPPP group (Supplementary Material S2). In addition to opioids, such as oxycodone and hydromorphone, oral anticancer drugs were frequently reported to cause suspected adverse drug reactions, especially in the BCPPP group.

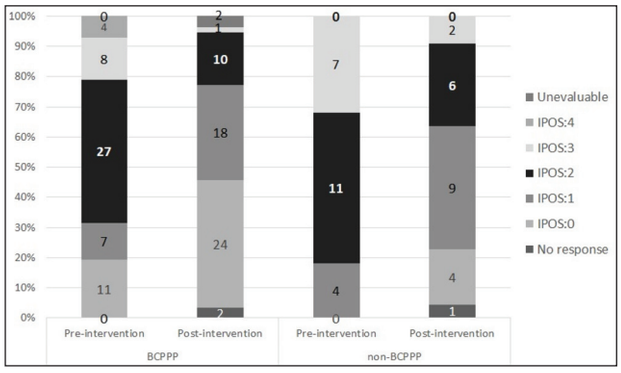

Fig. 2: Changes in integrated palliative care outcome scale (IPOS) values before and after intervention. Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy. IPOS:0 = not disturbing at all, 1 = slightly disturbing, 2 = moderately disturbing, 3 = very disturbing, and 4 = intolerable.

2.5. Follow-up after intervention for adverse drug reactions

Table 3 shows the status of adverse drug reactions and follow-up actions. In this study, both pharmacist groups had high acceptance rates of doctors' suggestions (BCPPP, 91.2%; non-BCPPP, 86.4%) for new drugs and changes in medications; however, the BCPPP group had a particularly high acceptance rate for changes in dosage and administration (Supplemental Material S3). The proposed drugs included laxatives such as magnesium oxide, sodium picosulfate, and naldemedine tosylate, and antiemetic

Table 3: State of intervention for adverse drug reactions by pharmacists

		Patients who received intervention from BCPPPs		Patients who received intervention from non-BCPPPs		P-value*
		n = 57		n = 22		
		n	%	n	%	
Detection of adverse drug reactions	Yes	26	45.6	12	54.6	0.616
	No	31	54.4	10	45.4	
Proposal of intervention for adverse drug reactions	Adopted and implemented	52	91.2	19	86.4	0.523
	Not adopted and not implemented	4	1.8	2	4.6	
	No response	1	7	1	9.0	
Status of follow-up for adverse drug reactions	Follow-up after implementation of interventions	33	57.9	1	4.6	<0.001
	Follow-up until end of adverse drug reactions	2	3.5	3	13.6	
	Follow-up after implementation of interventions and until end of adverse drug reactions	4	7.1	8	36.4	
	No follow-up	18	31.6	10	45.4	

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

agents such as olanzapine. Some pharmacists proposed steroids and other drugs (Supplemental Material S4). In the follow-up after the implementation of the suggestions, BCPPP professionals also actively intervened, with a significant difference ($P < 0.001$) between the two groups.

2.6. Effect of pharmacist intervention on adverse drug reactions

Figure 2 shows the integrated palliative care outcome scale (IPOS; 0 = not disturbing at all, 1 = slightly disturbing, 2 = moderately disturbing, 3 = very disturbing, and 4 = intolerable) for adverse drug reactions (constipation, nausea or vomiting, insomnia, somnolence, and others) before and after the intervention in the BCPPP and non-BCPPP groups. The number of patients with scores of 0, 1, 2, 3, and 4 before the intervention in the BCPPP group were as follows: 11 (19.3%), 7 (12.3%), 27 (47.4%), 8 (14.0%), and 4 (7.0%), respectively; after the intervention were: 24 (42.1%), 18 (31.6%), 10 (17.5%), 1 (1.8%), and 0 (0%) respectively. The number of patients with scores of 0, 1, 2, 3 and 4 before the intervention in the non-BCPPP group were as follows: 0 (0%), 4 (18.2%), 11 (50.0%), 7 (31.8%), and 0 (0%), respectively; after

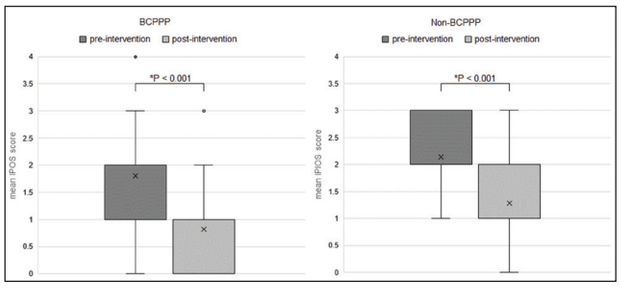

Fig. 3: Changes in integrated palliative care outcome scale (IPOS) values before and after pharmacist intervention. *Wilcoxon's rank-sum test. Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

the intervention were as follows: 4 (18.2%), 9 (40.9%), 6 (27.3%), 2 (9.1%), and 0 (0%), respectively. Only the BCPPP-intervention group had patients with a score of 4, which indicated unbearable pain. Figure 3 shows the differences in the IPOS scores before and after the intervention. The BCPPP pre-intervention mean score was 1.8 (standard deviation [SD]: 1.1), and the post-intervention mean IPOS score was 0.8 (SD: 0.9), indicating a significant improvement ($P < 0.001$). Similarly, the mean pre-intervention score in the non-BCPPP group improved significantly from 2.1 (SD =: 0.7) to 1.3 (SD =: 0.9) after the intervention ($P < 0.001$). We also examined the differences in the IPOS scores before and after the intervention between the two pharmacist groups and found no significant differences ($P = 0.826$).

2.7. Pharmacist confidence in intervention

This study also examined pharmacists' confidence in their ability to intervene in cases of adverse drug reactions. Although no significant difference was observed in the level of confidence between the two groups, positive responses for 'fairly confident' and 'somewhat confident' were higher among the non-BCPPP participants (BCPPP: 64.9%; non-BCPPP: 90.9%). Meanwhile, the negative responses for 'mostly not confident' and 'somewhat not confident' were higher among BCPPP participants, although both were low (BCPPP: 8.8%; non-BCPPP: 4.6%) (Supplemental Material S5).

3. Discussion

The most important finding of this study was that interventions by pharmacists to manage palliative pharmacotherapy drug reactions significantly improved the IPOS scores. In other words, patients' activities of daily living (ADL) improved when pharmacists managed drug reactions. Another important finding was that certified pharmacists intervened significantly more often than non-certified pharmacists in terms of both the number of patients receiving intervention and the number of drug reactions for which they intervened. In other words, certified pharmacists intervened more proactively in cases of drug reactions, suggesting that they had a higher awareness of the management of drug reactions in palliative pharmacotherapy. These results suggest that interventions by pharmacists certified in palliative pharmacotherapy may promote patient-centred multidisciplinary care and symptom relief.

Pharmacist interventions for palliative pharmacotherapy adverse drug reactions significantly improved the IPOS scores. Similar results were observed in both the BCPPP and non-BCPPP groups. Accordingly, this suggests the utility of pharmacist intervention in managing drug reactions, regardless of certification status. No significant differences were observed in the IPOS scores between the BCPPP and non-BCPPP groups. However, the BCPPPs provided interventions for patients with an IPOS score of 4, which indicates an extremely reduced ability to perform ADL. In other words, appropriate intervention in patients with an extremely impaired capacity to perform ADL can lead to symptom relief. Thus, one may interpret the data and associate BCPPPs with a higher awareness of adverse drug reactions than non-BCPPPs. Several studies have reported that the association between proactive interventions by palliative care pharmacists and patient outcomes varies across countries. In 2018, Atayee et al. reported that the length of stay (LOS), length from admission to palliative care consultation (LTC), and time from consultation to discharge or death (CTD) significantly improved when palliative care pharmacists were involved in the planning and administration of medications (Atayee et al. 2018). Another study also reported a significant reduction in the LOS when palliative care pharmacists were involved in the initial consultation within 72 h of admission and when they were the lead clinicians (Malotte et al. 2021). Furthermore, improvement in the severity of the patient's condition was achieved within the 24-h and 72-h assessment periods after receiving medication recommendation for pain, dyspnoea, anxiety, and constipation (Malotte et al. 2021). This study differs from previous studies in that the LOS, LTC, or CTD were not evaluated as outcomes. Instead, the IPOS scores were obtained and used to assess the patients' capacity to perform ADL. As no previous studies in Japan have investigated the intervention effects of the BCPPP, the results of this study have high clinical significance.

When the number of patients with adverse drug reactions and the number of adverse drug reactions were compared between the BCPPP and non-BCPPP groups, BCPPPs were more likely to intervene than non-BCPPPs in both cases. When the backgrounds of the patients in whom they intervened were compared, both the BCPPP and non-BCPPP interventions provided patients with the best supportive care. However, BCPPP interventions were provided more frequently than non-BCPPP interventions, particularly in patients who had received chemotherapy. Chemotherapy is generally administered in the early stages of the disease, and rarely at the end of life. These results suggested that BCPPPs intervened in the early stages of cancer. Early palliative care may prolong the survival of patients with advanced lung cancer (Temel et al. 2010). In this study, 63% of the patients treated by non-BCPPPs had lung cancer. Therefore, non-BCPPP interventions are necessary in the early stages of cancer. Among adverse drug reactions, both BCPPP and non-BCPPP interventions are frequently used for the symptomatic relief of constipation. Constipation can occur at approximately $1/50^{th}$ of the dose needed to achieve analgesia (Suzuki et al. 2006). As constipation is the most frequent opioid-induced adverse reaction, it was carefully monitored in both the BCPPP and non-BCPPP-intervention groups. In addition to constipation, nausea or vomiting, and somnolence, BCPPP intervention actively relieved increased serum creatinine, coughing, and other symptoms (Supplementary Material S2). These results suggest that BCPPP interventions help to treat symptoms that are difficult to identify by non-BCPPPs. Non-BCPPPs tended to be more confident about the intervention than the BCPPPs (Supplementary Material S5). This may indicate

that non-BCPPPs did not intervene in symptoms they were not confident about. Typical pharmacist interventions in palliative care include pain management and management of other symptoms such as hunger, dyspnoea, nausea, vomiting, constipation, excessive salivation, secretion management, delirium, and behavioural problems such as depression, anxiety, and insomnia (Moody et al. 2022). In the palliative care unit, patients received eleven different drugs, and each experienced five drug-related problems (DRPs). When pharmacists are intervening in DRPs, approximately 90% of cases can be resolved (Rémi et al. 2021). Clinically relevant DRPs are common in palliative care. Systematic assessments can support therapeutic decisions. Therefore, medication therapy should be optimised to improve symptom control and quality of life. Therefore, management of adverse drug reactions to opioids, non-opioids, and various drug-drug interactions is necessary.

Management of adverse drug reactions, especially laxative use, was particularly common in both the BCPPP and non-BCPPP-intervention groups. In 2021, Salmany et al. reported that the most common intervention by clinical pharmacists in hospice and palliative care was the recommendation or discontinuation of medication therapy (41%), followed by medication reconciliation (21.7%) and patient counselling (16.8%) (Salmany et al. 2021). In 2018, Naidu et al. reported positive clinical outcomes in patients cared for by palliative care pharmacists in terms of achieving pain goals and relieving nausea and dyspnoea symptoms by adjusting medication dosages (Naidu et al. 2018). The results of the present study are similar to those reported previously (Salmany et al. 2021; Naidu et al. 2018).

This study has some limitations. First, it did not consider the number of years since obtaining specialty certification in palliative care. Second, the minimum number of years of service for pharmacists without specialty certification in palliative care was two years, and for pharmacists with specialty certifications was ten years, indicating differences between the two. Third, survey respondents included pharmacists working in hospitals and community pharmacies. The amount of patient information handled by hospitals and community pharmacies differed, which may have affected the results. Fourth, the time context in which the presumed side effects occurred, including the context of drug treatment, is unknown. Fifth, this study evaluated the pharmacists' interventions in daily clinical activities, and the intervention conditions (including daily ward rounds and review of electronic patient charts) were not specified or investigated. Sixth, this study had a short survey response period and a low response rate, which may have necessitated prompting requests for survey cooperation or consideration to extend the survey period.

In conclusion, this study showed that pharmacists working in palliative care, with or without certification, have the potential to improve patients' ADL by intervening in cases of drug reactions. Furthermore, BCPPPs address a wide variety of adverse drug reactions experienced by many patients, regardless of the cancer type or severity. In addition, BCPPP interventions were mainly proposed to physicians with a focus on the modification of dosage and administration, and detailed follow-up interventions were implemented. These results suggest that BCPPP intervention for adverse drug reactions in palliative pharmacotherapy may lead to further enhancement of patient symptom management compared with interventions by non-BCPPPs. Further prospective cohort studies are required to clarify the usefulness of the BCPPP intervention by adding outcome measures, such as the length of hospital stay and achievement of symptom relief, such as pain, dyspnoea, and constipation.

4. Experimental

4.1. Study description, design, and participants

This was a multicentre prospective survey. Hospital and community pharmacists who were members of the JSPPCS participated in the research survey. Patients who experienced new drug reactions during the study period were enrolled and asked to respond to the requested survey items. For adverse drug reactions, the pharmacist intervened when the patient's symptoms were judged to be drug-related. Participants were enrolled from February to April 2022, and the survey response period was from February to May 2022. An e-mail explaining the purpose of the survey was sent to all members of the JSPPCS Research Committee, requesting voluntary cooperation. A questionnaire was sent to the pharmacists who agreed to participate. Google Forms, which is part of Google's free web-based Google Docs suite and can be used for survey creation and management, was used to administer all questionnaires. The JSPPCS maintains email addresses for its members. We attached the URL of the survey to the JSPPCS-registered email addresses and distributed it to all JSPPCS members. Participants were patients who experienced new drug reactions during the study period and answered the requested survey items. The follow-up period for each eligible patient began on the day the pharmacists initiated the intervention and ended at discharge, death, or after one month of intervention. If a participant was partially nonresponsive, missing data were presented as 'no response', and those participants were excluded from the study.

4.2. Survey items

The survey items included symptom severity at the start and at the end of the intervention, suspected drug use, proposed intervention, intervention location, belief in treatment contribution, total number of interventions, outcomes, and patient background. Participants were also asked about their place of employment, years of experience, and whether they were JSPPCS certified or had other academic certifications related to cancer treatment and palliative care.

4.3. Assessment methods

The primary endpoint was the impact of pharmacist intervention on adverse drug reactions. The secondary endpoints were the frequency of intervention, state of intervention such as the detection of adverse drug reactions, proposal of intervention for drug reactions, status of follow-up for drug reactions, and level of self-confidence in the intervention for drug reactions. The severity of adverse drug reactions was assessed by the participants using an IPOS before and after the intervention to determine the effect of their intervention.

The IPOS is a symptom assessment scale in palliative care that is used as a global standard in Europe, the U.S., Asia, and Australia because it provides a concise picture of patients' important concerns, including not only symptoms, but also anxiety, depressive mood, family concerns, and overall calmness (Schildmann 2016). The IPOS has been translated into Japanese and its reliability and validity have been confirmed (Sakurai 2019). Constipation, nausea/vomiting, insomnia, and somnolence were chosen as basic symptoms, and other physical symptoms were included under 'other' symptoms. Participants rated symptom intensity on a five-point Likert scale (0 = not disturbing at all, 1 = slightly disturbing, 2 = moderately disturbing, 3 = very disturbing, and 4 = intolerable). The option 'cannot be evaluated' was used if a post-intervention evaluation was not possible. Participants themselves, on the other hand, responded to the level of confidence in their contribution to the treatment on a six-point scale: 'very confident', 'somewhat confident', 'neither', 'somewhat not confident', 'not confident', and no response.

4.4. Statistical analysis

Descriptive statistics were used to evaluate the characteristics of the participants, clinical characteristics of the intervention patients, and the state of intervention for adverse drug reactions. The Wilcoxon rank-sum test was used to determine the number of patients who received the intervention, and the effect of the intervention on symptom improvement. Fisher's exact probability test was used to compare background and confidence in the interventions. The response format of the questionnaire was specified for each item as multiple responses were either allowed or not allowed. Statistical analysis was performed for the entire item when multiple responses were not allowed and for each option when multiple responses were allowed. Since the 'place of medical treatment' and purpose of admission were multiple response items, p-values were calculated for each item. JMP Pro version 16 (SAS Institute Inc., Cary, NC, USA) was used for all the analyses. Statistical significance was set at $P < 0.05$. significant.

4.5. Ethical considerations

This study was approved by the Ethical Review Committee for Clinical Research, Graduate School and School of Pharmaceutical Sciences, Osaka University (approval number: Yakuhito 2021-7, November 18th, 2021).

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Conflicts of interest: None declared.

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Supplementary material

Supplementary material S1

A) Frequency of interventions for patients in hospital ward in charge

Per week	All pharmacists n = 38		BCPPP n = 23		Non-BCPPP n = 15		P-value*
	n	%	n	%	n	%	
<1 time	9	23.7	7	30.4	2	13.3	
1 time	9	23.7	4	17.4	5	33.3	
2–4 times	10	26.3	5	21.7	5	33.3	0.604
≥5 times	3	7.9	2	8.7	1	6.7	
No response	7	18.4	5	21.7	2	13.3	

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

B) Frequency of interventions for patients in palliative care team

Per week	All pharmacists n = 32		BCPPP n = 19		Non-BCPPP n = 13		P-value*
	n	%	n	%	n	%	
<1 time	4	12.5	1	5.3	3	23.1	
1 time	11	34.4	6	31.6	5	38.5	
2–4 times	8	25	5	26.3	3	23.1	1.000
≥5 times	7	21.9	6	31.6	1	7.7	
No response	2	6.3	1	5.3	1	7.7	

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

C) Frequency of outpatient interventions

Per week	All pharmacists n = 38		BCPPP n = 23		Non- BCPPP n = 15		P-value*
	n	%	n	%	n	%	
<1 time	21	55.3	12	52.2	9	60	
1 time	5	13.2	4	17.4	1	6.7	
2–4 times	5	13.2	3	13.3	2	13.3	0.954
≥5 times	3	7.9	2	8.7	1	6.7	
No response	4	10.5	2	8.7	2	13.3	

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

D) Frequency of intervention for patients in palliative care hospital ward

Per week	All pharmacists n = 7		BCPPP n = 4		Non-BCPPP n = 3		P-value*
	n	%	n	%	n	%	
<1 time	0	12.5	0	0	0	0	
1 time	3	34.4	1	25	2	66.7	
2–4 times	2	25	1	25	1	33.3	1.000
≥5 times	1	21.9	1	25	0	0	
No response	1	6.3	1	25	0	0	

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

E) Frequency of intervention for patients in community pharmacies.

Per week	All pharmacists n = 16		BCPPP n = 5		Non- BCPPP n = 11		P-value*
	n	%	n	%	n	%	
<1 time	7	43.8	3	60	4	36.4	
1 time	3	18.8	1	20	2	18.2	
2–4 times	2	12.5	0	0	2	18.2	0.827
≥5 times	2	12.5	1	20	1	9.1	
No response	2	12.5	0	0	2	18.2	

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

F) Frequency of intervention for patients at home

Per week	All pharmacists n = 16		BCPPP n = 5		Non- BCPPP n = 11		P-value*
	n	%	n	%	n	%	
<1 time	3	18.8	1	20	2	18.2	
1 time	3	18.8	0	0	3	27.3	
2–4 times	4	25	1	20	3	27.3	0.778
≥5 times	3	18.8	1	20	2	18.2	
No response	3	18.8	2	40	1	9.1	

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

Supplementary material S2

Symptoms with pharmacist intervention

Breakdown of other symptoms	Patients who received intervention from BCPPPs n = 57	Patients who received intervention from non-BCPPPs n = 22
Constipation	15	8
Nausea or vomiting	6	2
Somnolence	6	5
Increased serum creatinine	4	0
Coughing (suspected interstitial lung disease)	3	0
Rash	1	2
Infusion puncture site pain	2	0
Neutropenia	2	0
Oedema	2	0
Insomnia	1	0
Thrombocytopenia	1	0
QT prolongation/bradycardia	1	0
Hypothyroidism	1	0
Increased liver enzymes	1	0
Suspected HBV reactivation	1	0
Stomatitis	1	0
Diarrhoea	1	0
Skin induration	1	0
Hand-foot syndrome	1	0
Dysgeusia	1	0
Peripheral neuropathy	1	0
Light-headedness	1	0
Osteoporosis/suspected bone fracture	1	0
Parkinson's syndrome	1	0
Delirium	0	1
Amnesia	0	1
Hypermagnesaemia	1	0
Hyponatraemia	0	1
Hyperkalaemia	0	1
Oliguria	0	1

Abbreviations: BCPPP; Board-Certified Pharmacists in Palliative Pharmacy

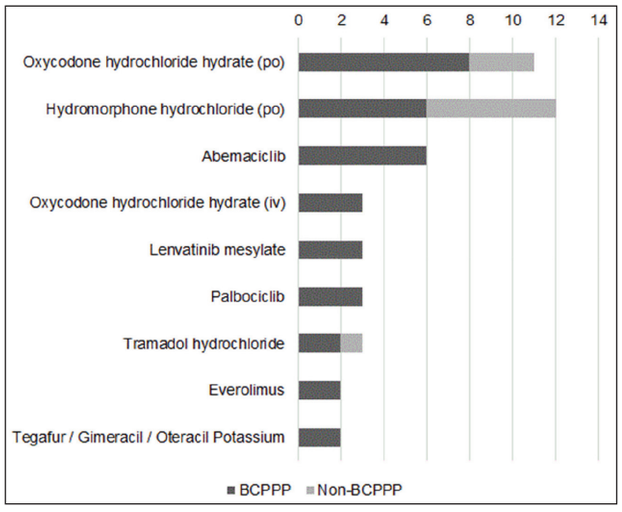
Supplementary material S3

Proposals of pharmacists for medical doctors

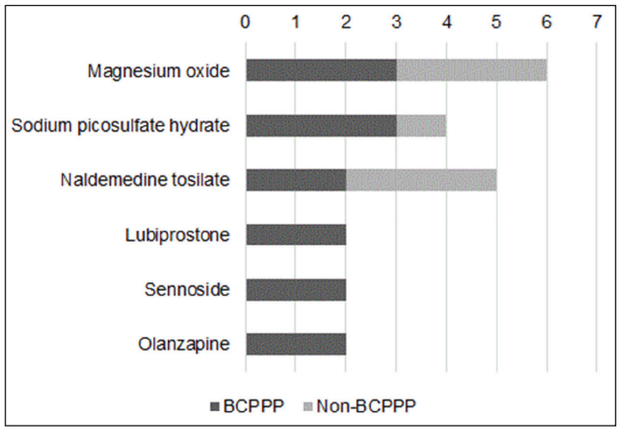
	Patients who received intervention from BCPPPs	Patients who received intervention from non-BCPPPs	P-value*
	n = 57	n = 22	
New drug proposal	23	8	0.802
Dosage and administration changes	17	2	0.077
Drug change/discontinuation/withdrawal	16	10	0.183
Drug continuation	3	2	0.614
Proposal of test	9	2	0.718
Change of dosage form	3	0	0.556
Other	3	0	0.556
No response	1	0	1.000

* Fisher's exact probability test.
Abbreviations: BCPPP, Board-Certified Pharmacists in Palliative Pharmacy

Supplementary material S4

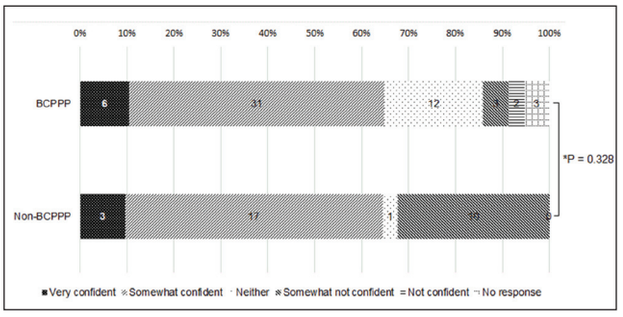


A) Suspected drugs with adverse drug reactions (≥2 cases).



B) Proposed medications (≥2 cases)

Supplemental material S5



Level of self-confidence in interventions for adverse drug reaction