



# Impact of individualized pharmaceutical care on efficacy and safety of opioid-tolerant outpatients with cancer pain: a multicenter randomized controlled trial

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**Background:** Managing cancer pain is a growing challenge. Individualized pharmaceutical care is particularly important for opioid-tolerant outpatients due to variation in terms of their knowledge about pain, treatment adherence, and risk of experiencing inadequate analgesia and severe adverse events. This study aimed to determine the influence of individualized pharmaceutical care on outcomes in opioid-tolerant outpatients with cancer pain.

**Methods:** A multicenter, open-label, randomized, controlled study was carried out. Opioid-tolerant outpatients experiencing chronic cancer pain and receiving sustained-release opioids were randomly assigned to the intervention group and the control group with a 1:1 ratio. The intervention group received individualized pharmaceutical care, while the control group received conventional care during 4-week period.

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The primary endpoint was medication adherence on the intention-to-treat (ITT) population. Secondary outcomes included the patients' knowledge of cancer pain and pain medications, pain score, frequency of breakthrough pain, quality of life (QoL) which were assessed on the ITT population. Adverse events were evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 4.0 on the per-protocol (PP) population.

**Results:** A total of 118 patients were enrolled, and 102 patients (51 in each group) completed the 30-day follow-up from six oncology centers in China. The proportion of patients adhering to opioid medication increased to similar levels in the two groups during the 4 weeks ( $P=0.149$ ). The intervention group had a significantly lower pain score at 4 weeks compared to the control group ( $P=0.015$ ), and the proportion of participants without breakthrough pain was significantly higher at 4 weeks than at baseline in the intervention group ( $P=0.029$ ), but not in the control group ( $P=0.322$ ). The two groups did not differ significantly in terms of QoL or adverse events.

**Conclusions:** Our results suggest that individualized pharmaceutical care can markedly reduce patient-related problems and significantly improve pain control in opioid-tolerant outpatients. These findings validate the recommendations to include clinical pharmacists in the management of cancer pain.

**Trial Registration:** ClinicalTrials.gov identifier: NCT03439904.

**Keywords:** Cancer pain; pharmacists; pharmaceutical service; opioids; outpatients

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## Introduction

Pain is one of the most distressing problems that compromise the quality of life (QoL) of cancer patients and their treatment outcomes (1,2). A substantial proportion of cancer patients (30–50%) report moderate to severe pain (3,4), and 40–55% of them consider their pain management to be inadequate (5-9). Opioid requirement and chronic pain are independent predictors of survival (10-15), and severe pain is associated with shorter survival, with mean hazard ratios ranging from 1.04 to 1.39 (10,12,14,15). Pharmacists can improve the management of cancer pain through interventions such as medication reviews, patient education, the detection and management of adverse drug reactions, and pain assessments (16-20), which are well accepted by physicians in the United States (US) and Canada (16).

The perception of inadequate pain control among patients can arise due to the application of inappropriate methods to assess pain, insufficient knowledge of cancer pain treatments, anxiety, depression, and non-adherence to analgesic regimens (21-24). Human genetic variations, such as  $\mu$ -opioid receptor 1 (*OPRM1*), *CYP2D6*, and catechol-O-methyl transferase (*COMT*), might be major contributors to the unpredictable clinical responses

to opioids (25). These multifaceted barriers highlight the need for multidisciplinary intervention during pain management.

Pharmacists can play an important role in such multidisciplinary approaches and have a positive impact on pain control and QoL in cancer pain patients (19,26-30). However, there are few randomized controlled studies investigating the effect of pharmacist intervention on patients with cancer pain. A multicenter randomized controlled study in Guangzhou China demonstrated that pharmacist-led medication education could result in improved pain control in patients with cancer. Nonetheless, this study only analyzed the impact of medication education provided by pharmacists (28). And other previous studies also have focused on only one or a few of the areas where pharmacists can contribute to cancer pain management, such as patient education, optimization of analgesic prescriptions, and monitoring of adverse drug reactions (16-20,26-30). However, clinical practice requires that pharmacists continuously engage in all of these activities in a way that takes into account each patient individually. Moreover, previous studies did not pay attention to the needs of specific cancer pain patients such as opioid-tolerant patients and outpatients for individualized services. In practice, individualized care is particularly important for

opioid-tolerant patients (those receiving at least 60 mg of morphine daily or an equianalgesic dose of another opioid for  $\geq 1$  week), who demonstrate greater variation than opioid-naïve patients in terms of their knowledge about pain, their treatment adherence, and their risk of experiencing inadequate analgesia and severe adverse events (31-33). More generally, individualized care is particularly important for outpatients who are not under constant medical supervision and may therefore be more likely to deviate from the recommended treatment (34).

Herein, we performed a prospective, randomized controlled study at six major oncology centers across China to evaluate the impact of individualized pharmaceutical care on outcomes related to cancer pain in opioid-tolerant outpatients. We focused on medication adherence, analgesic efficacy, QoL, and adverse events. We present the following article in accordance with the CONSORT reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4091/rc>).

## Methods

### *Study design and participants*

A multi-center, open-label, randomized controlled trial was performed at six Chinese oncology centers. The study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethical committees of each participating center (Table S1). All patients provided written informed consent.

The following inclusion criteria were used: opioid-tolerant patients with chronic cancer pain (pain that has lasted for  $\geq 3$  months) who were treated with sustained-release opioids [at least 25 mcg/h of fentanyl patch, 60 mg of morphine daily, or 30 mg of oral oxycodone daily (35)] were prospectively enrolled if they were at least 18 years old, their Karnofsky performance status score was  $\geq 50$ , and their estimated survival was at least 3 months.

Patients were excluded if they presented any of the following: treatment with patient-controlled analgesia, creatinine clearance rate  $< 15$  mL/min, alanine transaminase or aspartate aminotransferase  $> 10$ -fold the upper normal limit (36), pathological fracture, intestinal obstruction, severe infection, intractable constipation unrelated to opioids, cognitive impairment, or mental disorder.

Patients were removed from the study if they did not tolerate opioid therapy or were switched to non-sustained-

release opioids.

### *Randomization and interventions*

Patients were randomly assigned (1:1 ratio) to receive either pharmacist intervention or conventional care on an outpatient basis. Randomization was performed by Tong YH (Zhejiang Cancer Hospital) using the permuted block randomization method. The allocation was concealed using the sealed opaque envelopes. The intervention group received individualized pharmaceutical care based on a comprehensive assessment at baseline and during follow-up (Figure 1).

The first intervention was a face-to-face baseline assessment of the patients' knowledge about cancer pain and medication (Figure S1), medication adherence (37), and appropriateness of the analgesic scheme (Table S2). Educational materials on cancer pain management were also provided at the first intervention, which covered pain assessment methods, principles of cancer pain treatment, precautions when using analgesics, as well as the prevention and treatment of opioid-related adverse reactions. Subsequent interventions were conducted once a week by telephone over a 4-week period, with a second assessment conducted at the end of week 4. The follow-up period was set at 4 weeks to investigate whether pharmacist intervention could improve pain management in the short term. The conventional care included a telephone follow-up provided by a nurse within 1 week after the clinic visit and concise medication instructions along with drug dispensing in the outpatient pharmacy.

The control group underwent a similar baseline assessment, but they received conventional care without individualized pharmacist interventions during the remainder of the 4-week period (Figure 1).

### *Primary and secondary outcomes*

The primary outcome was medication adherence in the per-protocol (PP) population. Secondary outcomes included the patients' knowledge of cancer pain and medications, pain score, frequency of breakthrough pain, QoL, and adverse events.

The patients' medication adherence, pain score, QoL, and knowledge of cancer pain and analgesics were assessed by a face-to-face interview in the hospital on the first day and telephone intervention on day  $30 \pm 1$ . Adverse events related to pain treatment were collected on days 1,  $8 \pm 1$ ,

	Baseline		1 <sup>st</sup> week	2 <sup>nd</sup> week	3 <sup>rd</sup> week	4 <sup>th</sup> week	
	Baseline assessment	First intervention	2 <sup>nd</sup> intervention	3 <sup>rd</sup> intervention	4 <sup>th</sup> intervention	Final assessment	
Intervention group	<ul style="list-style-type: none"> <li>• Patients' knowledge of cancer pain and Adverse events medications</li> <li>• Pain score and frequency of breakthrough pain</li> <li>• Medication adherence</li> <li>• Quality of life</li> <li>• Appropriateness of prescription</li> <li>• Drug risk assessment</li> </ul>	Individualized intervention was conducted based baseline assessment results	<ul style="list-style-type: none"> <li>• Medication assessment and guidance</li> <li>• Efficacy evaluation and intervention</li> <li>• Adverse reaction assessment and guidance</li> <li>• Focus on medication issues identified in the previous assessment</li> </ul>			<ul style="list-style-type: none"> <li>• Patients' knowledge of cancer pain and medications</li> <li>• Pain score and frequency of breakthrough pain</li> <li>• Adverse events</li> <li>• Medication adherence</li> <li>• Quality of life</li> </ul>	
Control group	<ul style="list-style-type: none"> <li>• Patients' knowledge of cancer pain and medications</li> <li>• Pain score and frequency of breakthrough pain</li> <li>• Adverse events</li> <li>• Medication adherence</li> <li>• Quality of life</li> </ul>	Without individualized pharmacist interventions					

**Figure 1** Scheme of the individualized intervention provided by pharmacists to the intervention group.

15±1, 23±1, and 30±1.

**Medication adherence**

Pain medication adherence was assessed using the self-reported medication adherence scale (37,38). Total score ranges from 0 to 4: 0–1= low adherence; 2–3= moderate adherence; 4= high adherence.

**Knowledge about cancer pain and analgesics**

The patients' knowledge about cancer pain and medications was evaluated using a custom-designed questionnaire of 16 items involving knowledge about cancer pain, including its treatment and medications (Figure S1). Higher scores indicated better knowledge.

**Pain score and breakthrough pain**

Pain score during the last 24 hours was assessed using a numeric rating scale involving patients' self-reports on the intensity of their pain as a number usually ranging from 0 to 10, where "0" represents "no pain" and "10" denotes pain as "bad as it could be" (39). The frequency of breakthrough

pain during the last 7 days was also recorded.

**QoL**

QoL of patients was assessed using EuroQol-5 Dimension 3-Level (EQ-5D-3L) (40), which covers five domains: mobility, self-care, usual activity, pain, and anxiety/depression.

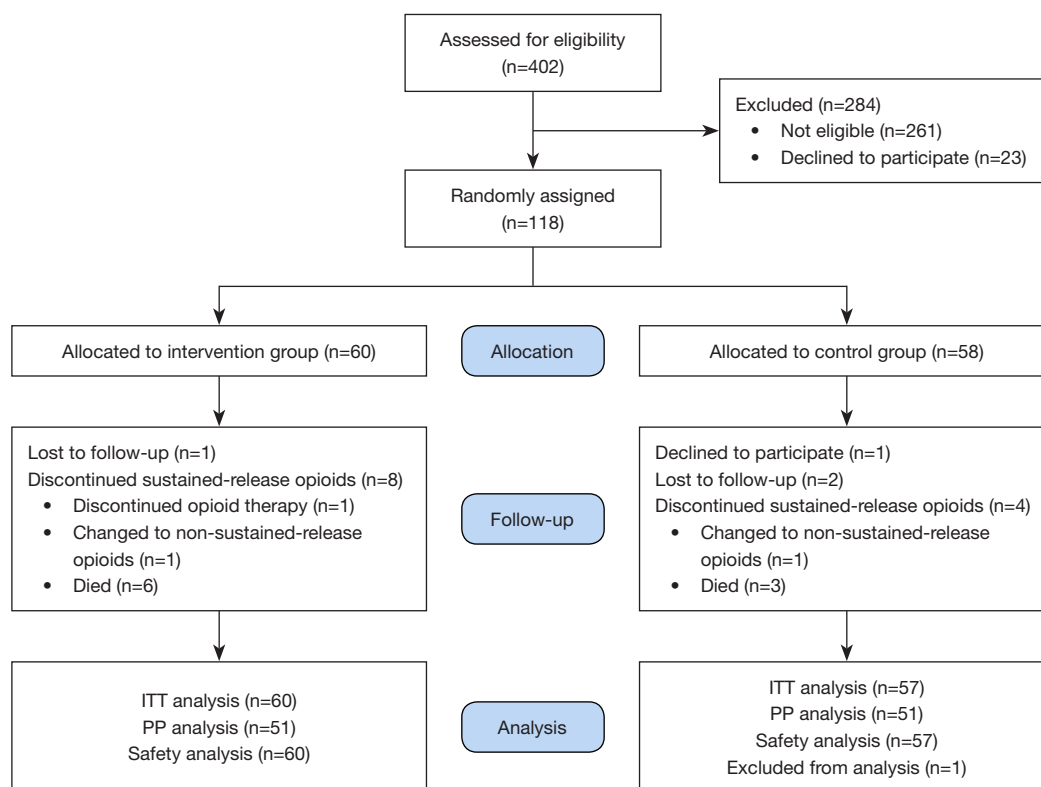
**Safety and tolerability**

Adverse events related to pain treatment and analgesics were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE, version 4.0) (41).

**Statistical analysis**

Assuming that the rate of high adherence to pain treatment at week 4 would be 15% higher in the intervention group than in the control group, we calculated that a sample of 118 patients would provide a power of 80% at a significance level (alpha) of 0.05, based on a two-sided, two-sample t-test.

Binary outcomes were reported as frequencies and



**Figure 2** Flow diagram of patient enrollment and analysis. ITT, intention-to-treat; PP, per-protocol.

proportions, and inter-group differences were assessed for significance using the chi-squared test. Continuous outcomes were reported as the median and interquartile range, and differences were assessed using the Mann-Whitney U test. Medication adherence, knowledge about cancer pain and pain medications, pain score, breakthrough pain, and QoL were compared between the two groups at baseline and week 4 on the intention-to-treat (ITT) population. Adverse events were analyzed in terms of frequency distributions on the PP population. If the proportion of missing data was greater than 40%, the data would not be included in the analysis, otherwise data were imputed using multiple imputation. Statistical calculations were performed using SPSS 23 (IBM, Chicago, IL, USA). A two-sided P value <0.05 was considered statistically significant.

## Results

From August 2018 to September 2019, we screened 402 outpatients with cancer pain for inclusion in this study, of which 118 were randomized into the intervention (n=60) or

control (n=58) groups (Figure 2). One patient in the control group declined to participate in the baseline evaluation, so 117 patients were included in the ITT population. Finally, 102 patients (51 in each group) completed the 30-day follow-up and were therefore included in the PP population.

Baseline demographic, clinical, and pain-related characteristics were generally balanced between the intervention and control groups in the ITT population (Table 1). Most patients in the control (80.7%) and intervention (70.0%) groups were prescribed sustained-release oxycodone. The remaining patients were prescribed transdermal fentanyl and sustained-release morphine.

During the individualized care, pharmacists provided various interventions aimed at remedying the lack of knowledge among patients about pain treatment and medications, lack of awareness about the treatment adverse reactions, inadequate medication adherence, and inappropriate analgesic regimens (Figure 3). During the 4 weeks of interventions, only seven patients received all five interventions, while 10 patients received four interventions. The three most frequent interventions were educating

**Table 1** Baseline clinicodemographic characteristics of the included opioid-tolerant cancer outpatients

Characteristics	Control group (n=57)	Intervention group (n=60)
Age (years)	62.0 (55.5–68.0)	61.5 (54.0–68.0)
Male	37 (64.9)	39 (65.0)
Primary diagnosis		
Lung cancer	23 (40.4)	20 (33.3)
Colorectal cancer	9 (15.8)	8 (13.3)
Breast cancer	1 (1.8)	6 (10.0)
Esophageal cancer	5 (8.8)	2 (3.3)
Liver cancer	4 (7.0)	2 (3.3)
Gastric cancer	2 (3.5)	3 (5.0)
Other	13 (22.8)	19 (31.7)
Disease stage		
II	2 (3.5)	4 (6.7)
III	0 (0.0)	1 (1.7)
IV	55 (96.5)	55 (91.7)
Karnofsky performance status score		
60	5 (8.8)	10 (16.7)
70	15 (26.3)	15 (25.0)
80	22 (38.6)	26 (43.3)
90	15 (26.3)	9 (15.0)
Bone metastases	28 (49.1)	29 (48.3)
Pain type		
Somatic	16 (28.1)	15 (25.0)
Visceral	3 (5.3)	9 (15.0)
Neuropathic	1 (1.8)	6 (10.0)
Mixed	37 (64.9)	30 (50.0)
Medications		
Sustained-release oxycodone	46 (80.7)	42 (70.0)
Sustained-release morphine	3 (5.3)	6 (10.0)
Fentanyl patch	8 (14.0)	12 (20.0)

Values are presented as n (%) or median (interquartile range).

the patients about pain treatment (n=58), education about pain medications (n=51), and resolving adverse drug reactions (n=33). Among all of the problems related to

pain management that were explored in this study, the proportions of problems from baseline to week 4 were more prevalent in the individualized intervention group than in the control group (Table S3).

Between baseline and week 4, both groups showed a significant improvement in pain score, breakthrough pain frequency, and knowledge about pain treatment (Table 2). The proportion of patients adequately adhering to opioid medication increased from 68.6% to 84.3% in the intervention group and from 60.8% to 72.5% in the control group, and the rate of high adherence at 4 weeks was similar between the groups (P=0.149). The proportion of participants who experienced breakthrough pain declined markedly from baseline to week 4 in the intervention group (P=0.029), but not in the control group (P=0.322).

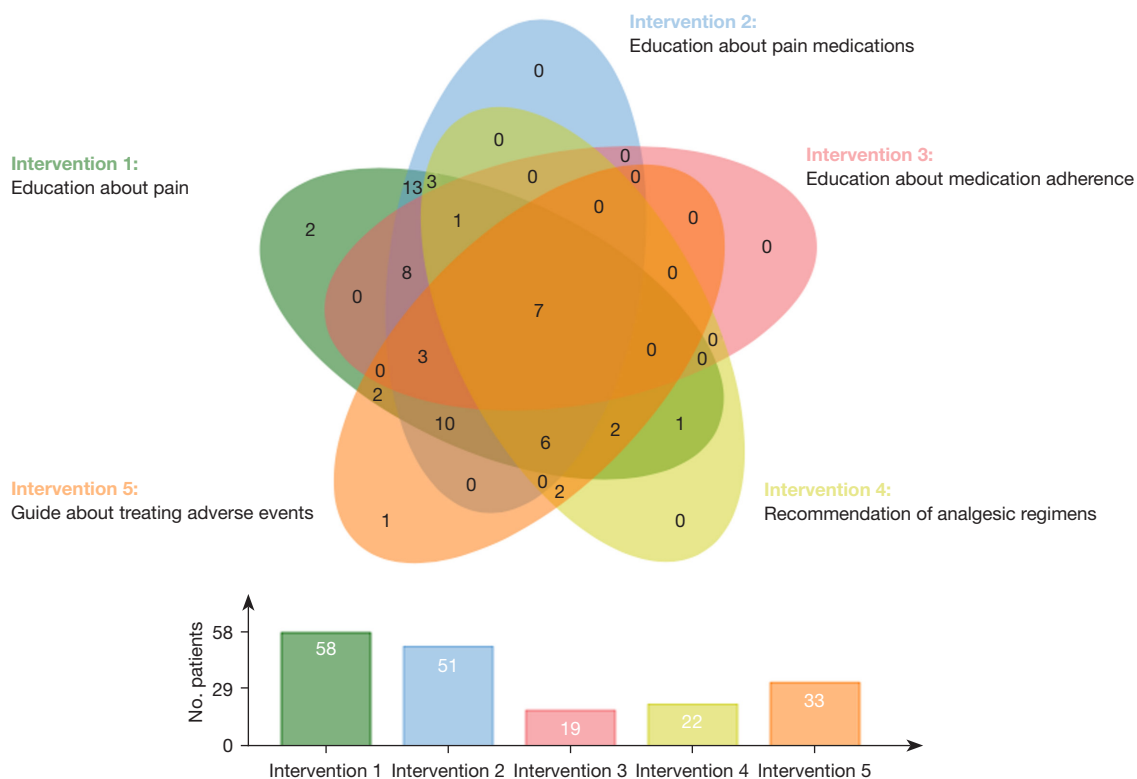
At week 4, knowledge about pain and medications was significantly greater in the intervention group than in the control group (P<0.001), and the intervention group showed a substantially lower pain score (P=0.015). The two groups did not differ notably in terms of the self-reported QoL (P=0.322) or the rates of adverse events (Table 3).

The oral morphine equivalent daily dose (OMEDD) was increased in both the control (median 120 vs. 120 mg, mean 153.5 vs. 168.8 mg) and intervention (median 90 vs. 120 mg, mean 120.0 vs. 145.1 mg) groups. However, there was no significant difference in OMEDD between the two groups at baseline (P=0.143) and at week 4 (P=0.283). And the increment of dose between two groups was also similar. (P=0.712).

## Discussion

In this study, we provided evidence that individualized pharmaceutical interventions, based on each patient's knowledge of pain and pain medications, can substantially improve pain control. Our study adds to a growing body of literature indicating that pharmacist-delivered interventions in patients with cancer pain can reduce the pain intensity and increase the level of knowledge related to pain management (19,20,27,28). Our findings validate the recommendations from the Chinese National Health Commission (42) and the US NCI (43,44) to include clinical pharmacists in cancer pain management.

A limited number of studies have investigated the role of pharmacists in the management of outpatients with cancer pain. Gagnon *et al.* (45) demonstrated that the participation of clinical pharmacists in palliative radiotherapy clinics plays a key role in holistic pain assessment and optimization



**Figure 3** The diverse interventions provided by pharmacists to the intervention group, and the numbers of patients receiving each intervention.

**Table 2** Intragroup and intergroup comparisons of the cancer pain-related outcomes in the control and intervention groups

Outcome	Control group (n=51)			Intervention group (n=51)			P for comparison between the two groups at baseline	P for comparison between the two groups at week 4
	Baseline	Week 4	P*	Baseline	Week 4	P*		
Patients reporting high adherence	31 (60.8)	37 (72.5)	0.208	35 (68.6)	43 (84.3)	0.062	0.407	0.149
Pain score	3.0 (3.0–5.0)	3.0 (3.0–3.0)	0.001	3.0 (3.0–4.0)	3.0 (2.0–3.0)	0.000	0.817	0.015
Patients with numerical rating scale score ≤3	28 (54.9)	42 (82.4)	0.003	27 (52.9)	48 (94.1)	0.000	0.843	0.065
Frequency of breakthrough pain per week	1.0 (0.0–10.0)	0.0 (0.0–5.0)	0.000	3.0 (0–10.0)	0.0 (0.0–5.0)	0.002	0.502	0.825
Patients experiencing no breakthrough pain during 1 week	22 (43.1)	27 (52.9)	0.322	19 (37.3)	30 (58.8)	0.029	0.545	0.550
Level of knowledge about pain and pain medications	7.0 (6.0–8.3)	8.1 (6.3–9.4)	0.000	6.4 (5.0–8.4)	11.9 (9.9–12.6)	0.000	0.402	0.000
QoL	0.769 (0.35–1.00)	0.782 (0.11–1.00)	0.390	0.775 (0.45–1.00)	0.782 (0.11–1.00)	0.162	0.732	0.871

Values are reported as n (%) or median (interquartile range), unless otherwise noted. \*, comparison between baseline and week 4. QoL, quality of life.

**Table 3** Comparison of the medication-related adverse events between the control and intervention groups

Adverse event	Control group (n=57)	Intervention group (n=60)	P
Constipation	24 (42.1)	24 (40.0)	0.817
Vomiting	6 (10.5)	5 (8.3)	0.685
Nausea	6 (10.5)	5 (8.3)	0.685
Somnolence	2 (3.5)	5 (8.3)	0.271
Urinary retention	5 (8.8)	2 (3.3)	0.215
Insomnia	0 (0.0)	1 (1.7)	0.328
Pruritus	1 (1.8)	0 (0.0)	0.303
Hoarseness	1 (1.8)	0 (0.0)	0.303
Sweating	1 (1.8)	0 (0.0)	0.303
Elevated liver function	2 (3.5)	0 (0.0)	0.143
Sychnosphygmia	1 (1.8)	0 (0.0)	0.303
Indigestion	1 (1.8)	0 (0.0)	0.303
Stomachache	1 (1.8)	0 (0.0)	0.303
Fatigue	1 (1.8)	0 (0.0)	0.303
Delirium	1 (1.8)	0 (0.0)	0.303
Dry mouth	1 (1.8)	0 (0.0)	0.303
Dizzy	1 (1.8)	0 (0.0)	0.303
Total	32 (56.1)	27 (45.0)	0.228

Values are presented as n (%), unless otherwise noted.

of treatment options, contributing to improved symptom control of patients receiving palliative radiotherapy. Yamada *et al.* (30) evaluated the impact of continuous pharmaceutical interventions on pain management and opioid-induced adverse effects in outpatients with cancer. Their results indicated that pain intensities significantly decreased following continuous pharmacist intervention. However, these two studies did not confirm whether pharmacist interventions contribute to pain remission without a control group. We designed this prospective, multicenter, randomized controlled study and evaluated the effect of individualized pharmaceutical care in outpatients with cancer pain in terms of their knowledge about pain treatment, medication adherence, frequency of breakthrough cancer pain, and QoL as well as the pain score and adverse events.

Medication problems and patient outcomes may be improved more efficiently if the interventions are tailored

to the patients' individual barriers (46). The individualized nature of the interventions in the present study meant that the patients received education and monitoring most closely suited to their specific pain management challenges. Thus, only seven patients received all five interventions that were planned in this study. The most frequent intervention in our study was education about pain and pain medications. The fact that many patients in our cohort did not require several of the other interventions may reflect that they had already received relevant education or pharmaceutical care.

Our results suggest that individualized pharmaceutical care can markedly reduce patient-related problems and significantly improve pain control for opioid-tolerant outpatients. At the same time, such care did not notably improve the adherence to opioid medication in our cohort. This apparently counterintuitive result may reflect the already high proportion of patients in our relatively small cohort who already had adequate adherence at baseline. It may also reflect the "Hawthorne effect", in which the baseline assessments of knowledge and medication adherence may have influenced the behavior of both the intervention and control groups (47). The Hawthorne effect may also help to explain why the control group showed improvement in medication adherence during the 4-week follow-up. Another possible explanation is that the OMEDD increased more in the intervention group than in the control group during the follow-up period. A fourth explanation is that the personalized follow-up by pharmacists fulfilled certain psychological and emotional needs in patients, which alleviated their perceived pain (48).

Our study has several limitations that should be noted. Firstly, we assessed the patients' knowledge about cancer pain and medications as well as the appropriateness of analgesic regimens using custom-designed questionnaires rather than standardized, validated instruments (Figure S1, Table S2). This may reduce the generalizability of our findings to other patient populations and healthcare contexts. Nevertheless, the questionnaires were developed by a multidisciplinary team of pain specialists and aligned with relevant national and international guidelines (49,50). Secondly, different pharmacists delivered interventions at the different study sites, although they followed the same overall intervention protocol. While variations in pharmacist attitudes and behaviors may have confounded our analysis, this situation reflects how interventions are deployed in the clinic, so our results are likely to have real-world relevance. Moreover, we did not perform corrections



for multiple comparisons.

## Conclusions

Our results suggest that individualized pharmaceutical care can markedly reduce patient-related problems and significantly improve pain control for opioid-tolerant outpatients. These findings validate the recommendations to include clinical pharmacists in the management of cancer pain.

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## Footnote

*Reporting Checklist:* The authors have completed the CONSORT reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4091/rc>

*Trial Protocol:* Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4091/tp>

*Data Sharing Statement:* Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4091/dss>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4091/coif>). All authors report that this study was sponsored by Mundipharma (China) Pharmaceutical. However, the sponsor did not participate in the conduct of the study and analysis of the data. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013), and all of the included research centers

provided ethical approval. Also, all participants provided written informed consent.

*Permission:* We have received license for the use of the medication adherence scale (Morisky, Green, Levine Scale) from the copyright holder.

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<b>Knowledge of pain treatment</b>						
1. Do you understand the impact of cancer pain?					Yes	No
2. Did you know that pain must be treated as early as possible?					Yes	No
3. Do you know how to assess pain?					Yes	No
4. Do you know how to deal with breakthrough pain?					Yes	No
5. Do you understand the aims of pain control?					Yes	No
<b>Knowledge of pain medications</b>						
6. Do you know the names of the pain medicines you are taking?					Yes	No
7. Are you afraid of developing an addiction?					Yes	No
8. Did you know that you should consult a healthcare professional before taking other drugs?					Yes	No
9. Did you know that sustained-release tablets should not be broken, chewed, or crushed; or that the fentanyl patch should not be punctured or cut?					Yes	No
10. Did you know that long-acting opioids should be taken regularly?					Yes	No
11. Did you know that you should not increase the dosage or frequency without first consulting a healthcare professional?					Yes	No
12. Indicate the opioid-related adverse reactions of which you are aware:						
<input type="checkbox"/> Nausea and vomiting	<input type="checkbox"/> Constipation	<input type="checkbox"/> Somnolence	<input type="checkbox"/> Delirium	<input type="checkbox"/> Dry mouth		
<input type="checkbox"/> Urinary retention	<input type="checkbox"/> Pruritus	<input type="checkbox"/> Excessive sedation	<input type="checkbox"/> Other	<input type="checkbox"/> None		
13. Indicate the opioid-related adverse reactions that you know how to treat:						
<input type="checkbox"/> Nausea and vomiting	<input type="checkbox"/> Constipation	<input type="checkbox"/> Somnolence	<input type="checkbox"/> Delirium	<input type="checkbox"/> Dry mouth		
<input type="checkbox"/> Urinary retention	<input type="checkbox"/> Pruritus	<input type="checkbox"/> Excessive sedation	<input type="checkbox"/> Other	<input type="checkbox"/> None		
14. Indicate which of the following medication-related situations require immediate medical attention:						
<input type="checkbox"/> Respiratory rate <10 breaths per minute	<input type="checkbox"/> The pupil becomes smaller	<input type="checkbox"/> Unconsciousness	<input type="checkbox"/> None			

**Figure S1** Custom-designed questionnaire to assess the patients’ knowledge about cancer pain and pain medications. Scoring of questions 1–11: a “yes” response was scored as 1 and a “no” response was scored 0; scoring of questions 12–13: “none” was scored as 0, and each other item was scored 0.1; scoring of question 14: “none” was scored as 0, and each other item was scored 0.3.

**Table S1** Ethics committee approvals

Research centers	Names of the ethics committees	Approval numbers	Approval date
Zhejiang Cancer Hospital	Ethics committee of Zhejiang Cancer Hospital (master)	IRB-2018-15	Jan.15, 2018
Jiangsu Cancer Hospital	Ethics committee of Jiangsu Cancer Hospital	2018-026	Mar. 29, 2018
Shandong Cancer Hospital and Institute	Ethics committee of Shandong Cancer Hospital and Institute	SDZLEL2018-009-02	Aug. 3, 2018
Fudan University Shanghai Cancer Center	Ethics committee of Fudan University Shanghai Cancer Center	1801180-9	Feb. 7, 2018
Anhui Provincial Cancer Hospital	Ethics committee of Anhui Provincial Cancer Hospital	2018-13	Mar. 6, 2018
Fujian Cancer Hospital	Ethics committee of Fujian Cancer Hospital	2018-023-01	Jun. 13, 2018

**Table S2** Assessment of the appropriateness of analgesic regimens

Question	Answer
Inappropriate opioid selection (e.g., no reason to choose fentanyl patch)	Yes/no
Excessive dosage of opioid analgesics	Yes/no
Insufficient dosage of opioid analgesics	Yes/no
Inappropriate use of adjuvant analgesics (e.g., exceeding dose limits of NSAIDs)	Yes/no
Inappropriate drug combinations (e.g., combinations of WHO-II and WHO-III opioids, two different NSAIDs)	Yes/no
There is a specific contraindication	Yes/no

Scoring: if all answers were “no”, the analgesic regimen was considered appropriate; otherwise, it was considered inappropriate. NSAIDs, non-steroidal anti-inflammatory drugs; WHO, World Health Organization.

**Table S3** Comparison of the potential barriers to cancer pain management between baseline and week 4

Potential barrier	Control group		Intervention group	
	Baseline (n=57)	At week 4 (n=51)	Baseline (n=60)	At week 4 (n=51)
Insufficient knowledge of pain treatment				
Did not understand the impact of pain on the primary disease	6 (10.5)	4 (7.8)	10 (16.7)	1 (2.0)
Did not know that pain must be treated as early as possible	3 (5.3)	1 (2)	8 (13.3)	0 (0.0)
Did not know how to deal with breakthrough pain	49 (86.0)	37 (72.5)	52 (86.7)	10 (19.6)
Did not know how to assess pain	37 (64.9)	27 (52.9)	40 (66.7)	8 (15.7)
Did not understand the aims of pain control	38 (66.7)	27 (52.9)	60 (100.0)	6 (11.8)
Insufficient knowledge of pain medications				
Did not know the names of the pain medicines taken	9 (15.8)	3 (5.9)	15 (25.0)	3 (5.9)
Fear of addiction	33 (57.9)	29 (56.9)	37 (61.7)	8 (15.7)
Did not know to consult a healthcare professional before taking other drugs	22 (38.6)	17 (33.3)	20 (33.3)	3 (5.9)
Did not know that sustained-release tablets should not be broken, chewed, or crushed; or that the fentanyl patch should not be punctured or cut	13 (22.8)	5 (9.8)	19 (31.7)	0 (0.0)
Did not know that long-acting opioids should be taken regularly	10 (17.5)	6 (11.8)	8 (13.3)	0 (0.0)
Did not know to consult a healthcare professional before increasing dosage or frequency	23 (40.4)	16 (31.4)	24 (40.0)	1 (2.0)
Insufficient knowledge about treating opioid-related adverse reactions				
Did not know how to treat nausea and vomiting	46 (80.7)	37 (72.5)	40 (66.7)	23 (45.1)
Did not know how to treat constipation	25 (43.9)	10 (19.6)	23 (38.3)	4 (7.8)
Did not know how to treat respiratory depression	53 (93)	40 (78.4)	49 (81.7)	14 (27.5)
Inadequate medication adherence				
Forgot to take medicine	NA	NA	7 (11.7)	3 (5.9)
Did not take medicine on time	NA	NA	15 (25.0)	5 (9.8)
Did not take the prescribed dose	NA	NA	6 (10.0)	0 (0.0)
Inappropriate prescription				
Inadequate opioid dose	NA	NA	19 (16.7)	0 (0.0)
Inappropriate opioid choice	NA	NA	2 (3.3)	0 (0.0)
Lack of adjuvant analgesic	NA	NA	1 (1.7)	0 (0.0)

Values are reported as n (%). NA, not applicable.