Outpatient Pain Medication Use:

An Electronic Daily Diary Study in Metastatic Breast Cancer

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Abstract

Context: Understanding cancer patients' everyday pain experiences and their concomitant use of pain medication may help identify ways to improve pain management among outpatients. **Objectives:** This study examined the between-person and within-person associations between pain intensity and analgesic use in metastatic breast cancer (MBC) patients. **Methods:** 53 women who were initiating treatment for MBC completed electronic diary assessments 6 times per day for 14 days. **Results:** The likelihood of taking medication was found to depend on patients' average pain levels and on whether their pain was better or worse than usual at the time. Patients who typically experienced moderate to high pain were more likely to be prescribed and to take analgesics than were patients who typically experienced low pain. However, these patients tended not to vary their medication use based on within-person fluctuations in pain. In contrast, patients who typically experienced low pain tended to increase their medication use at times when their pain was higher than usual, but were less likely to use medication than were patients who typically experienced higher levels of pain. **Conclusion:** Our findings provide some evidence that patients with advanced cancer tend to use their pain medications appropriately. Those with lower pain appear to be taking medications in response to increases in pain, whereas, patients whose pain is typically more intense may be relying on other cues to prompt them to take analgesic medication. Clinicians may need to be sensitive to individual differences in the factors associated with pain medication use in daily life.

Keywords*:* metastatic breast cancer; electronic diary; pain intensity; analgesic use; ambulatory assessment.

Introduction

Pain is one of the most feared and burdensome symptoms associated with cancer and its treatment. Meta-analytic estimates suggest that pain is experienced by 58-75% of patients with advanced, metastatic, or terminal cancer (1,2). Finding ways to relieve this pain could significantly improve multiple aspects of their quality of life (3–5). Although pharmacological treatments are not necessarily appropriate under all circumstances, they provide substantial relief to many advanced cancer patients (6). However, a recent systematic review suggests that one third of cancer patients do not receive pain medication proportional to their pain intensity (7). Many advanced cancer patients also report challenges in adhering to their prescribed treatments (8–10). A better understanding of how cancer patients use pain medications in their everyday lives may help identify ways to optimize their use.

Most of our knowledge of pain in the context of advanced cancer has come from cross-sectional studies that use global retrospective measures (11–14). Cross-sectional studies can only describe between-person differences in pain and analgesic use. That is, they can tell us whether people who tend to experience more pain tend to take more pain medication (11). In contrast, daily diary or experience sampling studies that assess pain and analgesic intake close to their real-time occurrence are less prone to recall bias and can be used to capture both between-person differences and within-person processes (15,16). This type of intensive longitudinal design can show not only whether people who experience more pain take medication more often (i.e., between-person differences), but also whether people increase their medication intake at times when their pain is worse than usual (i.e., within-person differences). Further, it can inform regarding whether some people are more likely than others to increase their medication intake in response to within-person fluctuations in pain.

We conducted an electronic daily diary study to tease apart the between-person and within-person associations between pain intensity and analgesic use in metastatic breast cancer (MBC) patients. MBC provides an excellent context in which to study the association between pain intensity and analgesic use because many of these patients experience severe pain, and effective pain management is a central concern in maintaining their quality of life (17). Diary studies of other oncology and chronic pain populations suggest that pain intensity is an important predictor of analgesic intake in daily life (10,18–20). However, some of these studies have confounded between-person and within-person associations (18,20), or reported the association at only one level of analysis (19). Given that between-person and within-person associations are not necessarily the same and can even lead to discrepant findings (21), it is important not to confound them. Additionally, the size of the within-person association between pain and analgesic intake can vary across individuals (19), but less is known about the factors that might explain these individual differences.

Based on existing cross-sectional and daily diary research (10,11,19), we hypothesized that MBC patients with higher pain would take pain medication more often on average (Hypothesis 1), and that patients would be more likely to take pain medication at times when they experienced higher-than-usual pain (Hypothesis 2). We also examined whether the tendency to take more medication at times when the pain was higher than usual varied across individuals as a function of their average pain levels. We chose to focus on pain as the primary symptom driving analgesic intake because this is the primary symptom these medications are designed to treat.

Methods

Participants and Procedure

Data for this study were drawn from a larger study of spousal relationships and MBC pain that was conducted at a comprehensive cancer center in the southwestern United States (22–26). All procedures were approved by the appropriate Institutional Review Boards, and all participants provided written informed consent.

Patients were identified through medical chart review and were eligible if they 1) were female patients who were initiating any line of therapy for MBC; 2) had a physician-rated Eastern Cooperative Oncology Group (ECOG) performance status score ≤2 (ECOG scores range from 0=fully ambulatory and able to carry on all pre-disease performance without restriction, to 5=dead – a score of 2 means that the patient is ambulatory and capable of all self-care but is unable to perform any work activities); 3) rated their average pain as ≥1 on the Brief Pain Inventory (BPI)(27), where 0=no pain and 10=worst pain imaginable; 4) could speak and understand English; and 5) had a male partner (spouse or significant other) with whom they had lived for at least one year[1]. All consecutive patients who met the eligibility criteria were approached along with their partners, and asked to participate by study staff during their routine clinic visits. Couples who participated in the parent study could also participate in an additional optional procedure involving electronic diary assessments. Data from these electronic diaries are presented here.

Ninety-four consecutive MBC couples who had agreed to participate in the parent study were approached to participate in the electronic diary procedure. Fifty-nine of these couples (62.8%) agreed to participate. Reasons for refusal included: patient or partner disinterest (57.1%), perceived burden of completing the optional procedure or conflict with work

[1] One of the goals of the larger parent study was to examine coping and relationship processes in women with MBC and their husbands, therefore this inclusion criterion was added.

responsibilities (40%), and a lack of perceived personal relevance of the study (2.9%). Because the focus of the current investigation was on the association between pain intensity and pain medication intake, and because these items were only assessed for patients, only patient data are reported here.

Comparisons were made between patients who refused and those who participated based on available data for age, ECOG performance status, race, average pain at time of recruitment (assessed by the Brief Pain Inventory), and primary metastatic site. Significant differences were found for age ($t(91)=3.98$, $p<0.001$) and pain ($t(82)=5.55$, $p<0.001$). Specifically, patients who agreed to participate were younger ($M=49.38$, $SD=10.76$) than those who refused ($M=58.11$, $SD=9.30$), and patients who agreed to participate had higher ratings of pain ($M=4.41$, $SD=3.01$) than those who refused ($M=1.12$, $SD=0.43$).

Participants were each provided with their own password-protected electronic diary (ED). The diaries were programmable Palm Tungsten E or E2 computers (32 MB RAM) weighing 4.7 ounces and powered by rechargeable lithium ion batteries. Participants used a stylus to touch fixed-response options in answer to questions presented in a fixed order on a 2.4-inch transreflective liquid crystal color display (resolution, 320×320 pixels). Participants were trained to use the EDs and received follow-up telephone calls within 3 days of taking them home. In 6 cases, no usable data could be recovered from the ED; thus, the final sample comprised 53 participants[2].

Participants were prompted to complete ED assessments 6 times a day for 14 consecutive days (84 total assessments). An alarm sounded to cue participants that it was time to complete

[2] Initially data from 54 patients was recovered. However, the files for one patient were overwritten, leaving useable data for 53 patients.

the ED assessment. Reminder alarms would sound every 5 minutes for 15 minutes or until the participant completed the diary assessment. If a participant did not respond to the alarms prompting her to complete the questionnaire, she could not complete it at another time. To keep the length of the assessment day and the intervals between assessments consistent across participants, diaries were programmed to prompt assessments by generating alarms between 9 am and 9 pm. A stratified-random sampling scheme was used to ensure that moments sampled within blocks were random and that the entire waking day was covered. The minimum time between assessments was 30 minutes. The morning assessment was randomly scheduled between 9:00 am and 10:00 am (Time 1). Four daytime assessments followed; one occurred between 10:30 am and 12:30pm (Time 2), two occurred between 1:00 pm and 5:00 pm (Time 3 and Time 4), and one occurred between 5:30 pm and 7:30pm (Time 5). A final evening assessment occurred between 8:00 pm and 9:00 pm (Time 6). Depending on the type of assessment (morning, daytime, or evening), the time needed for completion was 2 to 5 minutes. Participants received gift cards (up to $80) based on the percentage of assessments they completed. On average participants completed 59 (70%) of the 84 possible diary assessments (median = 64; a range = 8 to 82 assessments per person).

Measures

Pain. In each ED assessment, participants rated their pain at that moment ("right now") on an 11-point numeric rating scale from 0 (no pain) to 10 (worst pain imaginable) using a single-item from the Brief Pain Inventory (BPI) (28).

Pain Medication Use. At enrollment patients were asked to report medications they were prescribed. These reports were verified by medical records whenever possible. In each ED assessment, regardless of whether the patient indicated if she was in pain, patients were

prompted to respond to the question, “Since your last assessment, did you take any medicine for your pain” Response options were yes/no. If patients answered yes, they were subsequently asked, “What type of medicine did you take?” Response options were: prescription medication, over-the-counter medication, or both.

Statistical analysis

We used mixed effects logistic regression to examine how within-person changes and between-person differences in pain intensity were associated with the probability of taking medication at each measurement occasion. The analyses were run in R using the *lme4* and *lmerTest* packages (29–31). Patients were asked if they had taken any medication since the last assessment; therefore, the first assessment of the day captures any medication taken since the last assessment of the previous day (the time interval from 9pm to 9am the next day). Because we were interested in understanding the influence of pain intensity on medication use throughout the day, we focused our analyses on the daytime and evening assessments where current pain intensity could be used to predict subsequent pain medication use as reported at the next assessment a few hours later.

To examine whether people who tend to experience higher levels of pain intensity are those who tend to take medication more often (Hypothesis 1), we computed the mean pain intensity for each participant (person means) across measurement occasions and used that to predict between-person differences in the probability of medication intake. To examine whether patients were more likely to take medication following times when their pain was more intense than it usually was for them (Hypothesis 2), we subtracted each person’s mean pain intensity score from their observed pain intensity scores and used these person-mean centered scores to predict within-person fluctuations in the probability of medication intake. To examine whether

the within-person relationship between pain intensity and probability of medication intake depended on the person's typical level of pain, we computed a multiplicative interaction term (i.e., person's mean pain × within-person deviations in pain). Prior to computing the interaction term, the person means for pain intensity were centered on the sample mean (M = 1.67). This means that the lower order coefficients in Table 1 can be interpreted in terms of the average participant on the typical day.

Given that time of day and patient's prescription status were associated with pain intensity and medication intake, both variables were included as covariates. Time of day was centered such that the earliest time point is coded -2 and the latest time point is coded +2. Prescription status was dummy coded with participants without a prescription as the reference group (no prescribed medication for pain = 0; prescribed pain medication = 1). Prescription status was missing for one participant. To retain all observations from this participant, the missing value was replaced with the sample mean. Neither control variable was found to moderate the association between pain and medication intake.

Results

Sample characteristics

Patients were predominantly white (85%), well-educated (86% had at least 2 years of college study), and retired or unemployed (61%). Average age was 49.38 years, (SD=10.76; range 30 to 73 years). Although all patients were beginning treatment (any line of therapy) for stage 4 breast cancer at the time of study entry, disease stage at initial cancer diagnosis included stage 1 (13.56%), stage 2 (28.81%), stage 3 (15.25%), and stage 4 (42.37%). The average length of time since initial cancer diagnosis was 4.75 years (SD=4.5; Range 1 month to 19.5 years). Primary metastatic sites were: bone (56%), lung (22%), liver (19%), and brain (3%). Regarding

treatment, 83% of patients were beginning chemotherapy, 15% hormonal therapy, and 2% radiation. Of the 58% of patients with a prescription for pain medication, 87% were prescribed opioids, 13% were prescribed non-opioid analgesics, 3% were prescribed anticonvulsants, and 3% were prescribed benzodiazepines, and 19% were prescribed multiple medications.

Descriptive results

To examine the relationship between momentary pain intensity and subsequent medication intake throughout the day, we used a total of 2106 lagged pairs of observations from 53 patients (median number per person = 41, range = 4-66). The number of assessments completed per participant was unrelated to their average pain intensity scores or frequency of medication intake. The average pain rating was 1.67 (between-person SD=1.85, within-person SD=1.28)[3]. Participants reported having taken pain medication since the previous entry on 15% of assessments (n= 322). Prescription medications were taken 77% of the time (n=248) and over-the counter-medications (OTC) were taken 27% of the time (n=89). On 5% of occasions (n=15), both prescription and OTC medications were taken. On average, participants who were prescribed medications for pain reported significantly higher levels of pain (b=1.01, t(51)=2.00, p=.05) and took medications more often than did participants without a prescription (OR=4.40, z=2.90, p=.004).

Association between momentary pain and subsequent medication use

The results of the mixed effects logistic regression model predicting pain medication use are summarized in Table 1. As hypothesized, both average levels of pain intensity (OR=1.73, z=5.36, p<.001) and within-person fluctuations in pain intensity (OR=1.41, z=6.41, p<.001) were

[3] To account for the nesting of observations within persons and differences in the number of observations per person, we used an intercept only linear mixed effects model with no predictors to estimate mean pain intensity and the variance within- and between-persons.

associated with greater medication use. However, the significant interaction between Person mean pain and within-person deviations in pain (OR=0.93, z=-3.24, p=.001) indicates that the size of the within-person effect depended on how much pain the patient typically experienced. Figure 1 illustrates this finding. The dashed line in Figure 1 shows that patients who typically had higher levels of pain intensity tended to take pain medication more often and the solid lines in Figure 1 show the change in likelihood of taking medication depending on whether the pain is less intense than usual (1 SD below the participant's mean) or more intense than usual (1 SD above the participant's mean). For the average patient whose mean pain was 1.67 (the sample mean), pain that was 1 point worse than usual was associated with 1.41 times higher odds of taking pain medication (OR=1.41, z=6.41, p<.001). However, patients who typically experienced moderate or severe pain (mean pain score > 4.6/10) were not significantly more likely to take medication when their pain was one point worse than usual compared to times when they were experiencing their typical levels of pain.

Discussion

Our findings suggest that both between-person differences in average pain and within-person fluctuations in pain affect the use of medication to treat that pain. For patients who usually experienced low levels of pain, within-person increases in pain were associated with a significantly higher likelihood of taking medication. On the other hand, patients who usually experienced moderate to high levels of pain were more consistent in their medication use (e.g., purple line on Figure 1). Even when they experienced some pain relief and were in less pain than usual, they tended to take medication as usual. Their pain may still have been intense enough to motivate them to take medication. For patients whose pain is typically less intense, relative increases in their pain may cue or motivate them to take analgesic medication. Patients whose

pain is typically more intense may be relying on other cues to prompt them to take analgesic medication. Future research using daily dairy methods is needed to identify what these cues might be. They could include contextual factors (e.g., daily activities) or features of the medication itself (e.g., administration schedule). Nevertheless, clinicians may need to be sensitive to individual differences in the factors associated with pain medication use in daily life.

In our study, the overall levels of pain intensity and medication intake were relatively low. This provided a more conservative test of our hypotheses, but may also reflect some degree of success in terms of pain management. No pain was reported on over 40% of all momentary assessments. This could indicate that, at least for some patients, pain is a relatively infrequent symptom or that they had achieved moments of pain relief. Nevertheless, many patients did report experiencing moderate to severe levels of pain. At enrollment, the average patient reported moderate pain (M=4.41) and all patients reported at least some pain (BPI $\geq$ 1). Momentary pain levels reported in the electronic diaries were significantly lower on average (M=1.67). This finding adds to research indicating that global retrospective measures and diary assessments capture different information (15,32). Given the unique information they capture, electronic diaries could be added to the tools clinicians use for pain assessment and treatment (33–35).

The current opioid crisis in the United States (36–38) has raised concerns about the misuse and abuse of opioid medications in the oncology setting (39,40). All medication present some risk and clinicians must balance the risks against the potential benefits for their patients. Our findings provide some evidence to suggest that pain medications are being used appropriately in daily life among MBC patients. Those patients who experienced more severe pain on average were the ones who were more likely to be prescribed medications for pain and to take pain medications consistently throughout the day. However, the current investigation

focused on predicting the use of any type of pain medication in daily life. Studies of larger samples are needed to examine the extent to which the predictors of medication intake vary as a function of the type of mediation used (e.g., opioids vs. non-opioid analgesics; ATC vs. PRN), and the extent to which our findings generalize to other chronic pain or cancer populations.

We examined a stage of cancer that has received very little attention in the literature on quality of life. However, adherence to the electronic diary procedure was lower than researchers typically report outside the oncology setting (41). Decreased rates of adherence in this study may be because patients were initiating treatment for MBC, had increased demands on their time, and were experiencing pain and cancer-related symptom burden. Participants were selected from a larger study and were all married or living with a partner. They were younger (M=49.38 years) than the typical breast cancer patient (median age for a breast cancer diagnosis is 61 years) (42). Older patients may have declined participation because they were not as comfortable with the computerized assessments. Thus, caution must be exercised in generalizing beyond the sample enrolled in this study.

In conclusion, our study using repeated electronic diary assessments has provided some unique insights into the relationship between pain and analgesic use in the daily lives of women with MBC. When choosing among different treatment approaches, clinicians may need to be sensitive to not only individual differences in the average level of pain, but also how this might affect the within-person factors associated with pain medication use in daily life.

Disclosures

The authors have no conflicts of interest to disclose.

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Table 1. Mixed effects logistic regression predicting medication intake

	Odds of taking pain medication since previous diary assessment				
Fixed effect parameter	b	*SE*	*z*	*p*	*OR*
Intercept	-3.08	0.33	-9.25	<.001	0.05
Time of day[1]	0.17	0.05	3.37	.001	1.19
Analgesic prescription	0.82	0.42	1.95	.049	2.26
Person mean pain	0.55	0.10	5.37	<.001	1.73
Within-person deviations in pain[2]	0.34	0.05	6.41	<.001	1.41
Person mean pain × within-person deviations in pain	-0.07	0.02	-3.24	0.001	0.93
Random effect parameters[3]					
Intercept variance	1.35				

1. Time of day is centered such that the earliest time point is coded -2 and the latest time point is coded +2. 2. Between-person pain is centered at 1.67 (the sample mean), so this is the within person slope for the typical patient whose mean pain score is 1.67. 3. Only random intercepts were estimated, because when random intercepts and random slopes were included, the model failed to converge.

Figure

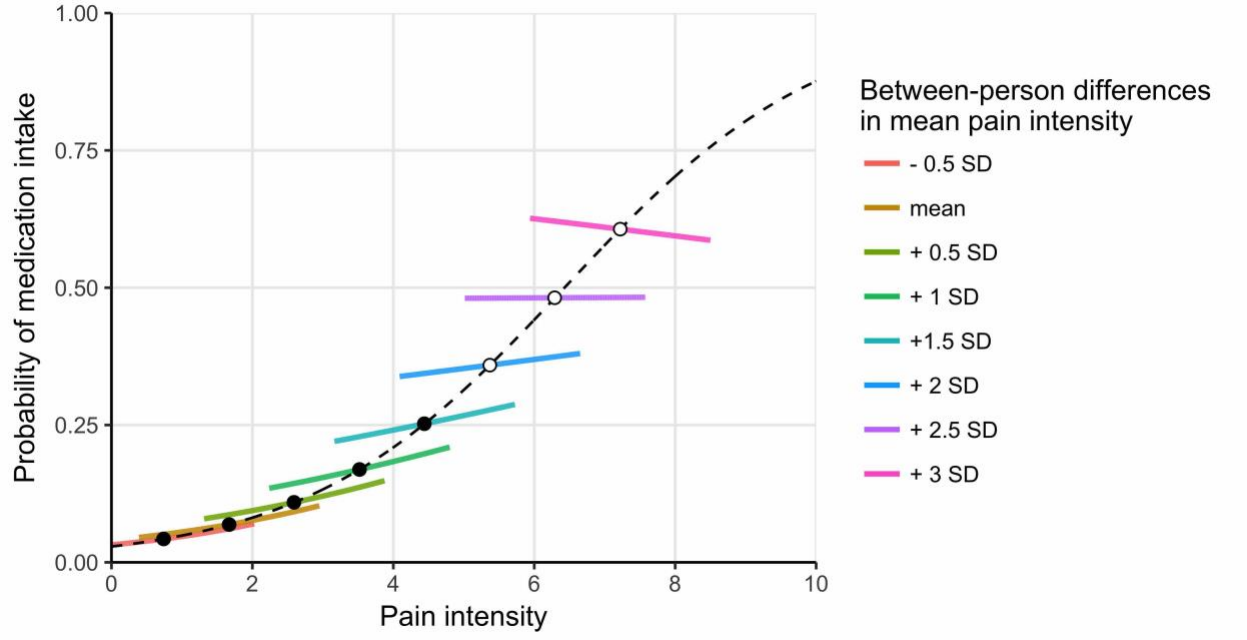

Figure 1. Relationship between pain intensity and medication intake. The dashed black line depicts the between-person relationship between pain intensity and medication use. The solid lines show the within-person relationship (from 1 SD lower than usual to 1 SD higher than usual) between current pain intensity and subsequent medication use for the typical participant at different levels of mean pain intensity. The solid dots denote significant within person slopes ($p < .05$) for the typical patient with that level of mean pain intensity. The hollow circles denote non-significant within-person slopes.