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Trajectories and Predictors of Symptom Occurrence, Severity, and Distress in Prostate Cancer Patients Undergoing Radiation Therapy

by

Katie Knapp

THESIS

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Trajectories and Predictors of Symptom Occurrence, Severity, and Distress in Prostate Cancer Patients Undergoing Radiation Therapy

Katie Knapp

ABSTRACT

Context. Radiation therapy (RT) is a common treatment for prostate cancer. Despite available research, prostate cancer patients report that information about side effects is their most important unmet need. Additional research is needed that focuses on specific dimensions of the patient's symptom experience.

Objectives. The study's purposes were to evaluate the trajectories of occurrence, severity, and distress of the six most prevalent symptoms reported by patients undergoing RT for prostate cancer and evaluate the effects of selected demographic and clinical characteristics on these trajectories.

Methods. Patients completed the Memorial Symptom Assessment Scale eleven times before, during, and after RT. For problems with urination, pain, lack of energy, feeling drowsy, difficulty sleeping, and diarrhea, the trajectories of occurrence, severity, and distress were evaluated using multilevel generalized linear models.

Results. Across all three dimensions, pain, lack of energy, feeling drowsy, and difficulty sleeping followed a decreasing linear trend. Problems with urination and diarrhea demonstrated more complex patterns of change over time.

Conclusions. While longitudinal data on pain, lack of energy, feeling drowsy, and difficulty sleeping are limited, they are highly prevalent symptoms in these patients. In addition, diarrhea becomes a significant problem for these patients over the course of RT. Various demographic and clinical characteristics effect the trajectories of the various symptoms differentially.

Key Words: prostate cancer, radiation therapy, piecewise modeling, symptom trajectories, symptom predictors, occurrence, severity, distress, pain

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INTRODUCTION

Prostate cancer accounts for one in four new cancers diagnosed in men annually in the United States (U.S.), with an estimated 217,730 new diagnoses anticipated for 2010 alone.(1) Because age is the most important risk factor for the development of prostate cancer and the number of Americans over the age of 65 is expected to more than double in the next 40 years,(2) it is reasonable to anticipate that the number of men living with prostate cancer will also increase dramatically during that time. When faced with treatment decisions, many of these men will choose to undergo radiation therapy (RT). Despite the fact that trajectories for common symptoms (e.g. urinary problems) associated with this treatment have been established, prostate cancer patients report that information about side effects is their most important unmet need.(3)

The National Cancer Institute recognized this unmet need by establishing “patient-centered communication” as a priority area for research.(4) While a plethora of information is available about symptoms related to RT, additional research is needed that is focused on individual patient’s experiences. For example, no study has compared multiple symptom trajectories among patients with prostate cancer to determine which symptoms are the most common. Much of the research on symptom trajectories was done with the goal of evaluating for differences across treatment modalities for prostate cancer, with particular emphasis on urinary, bowel, and sexual functioning.(5-10)

For example, data from a series of studies found that patients who underwent RT had more bowel and bladder problems at the initiation of RT than

patients who underwent radical prostatectomy (RP).(5, 8, 9) While men who underwent RP had a sharp increase in urinary problems that decreased over time,(6-9) the occurrence of urinary problems after RT increased(5, 7, 8) or decreased then increased (9) over time. Additional work found that a higher percentage of patients who had a RP reported more urinary incontinence issues than those who had RT, where a higher percentage of RT patients reported more obstructive and irritative symptoms.(8) The majority of the studies that evaluated bowel dysfunction found higher occurrence rates following RT compared to RP.(6-8) Both treatments resulted in decreases in sexual function. However, patients who underwent RP reported a more precipitous decline.(6, 7, 9, 10)

Five studies were found that evaluated changes in the occurrence and/or severity of pain and fatigue in prostate cancer patients during and after RT.(11-15) In one study,(12) no changes in pain severity occurred over the course of RT. In contrast, Lips et al.(13) reported that changes in pain intensity after one month of treatment was dependent on the type of RT received. In terms of fatigue, in two studies,(11, 12) fatigue increased over the course of RT but returned to baseline shortly after completion of treatment. In contrast, Monga et al.(15) found that fatigue scores remained significantly elevated for 12 months or more after RT. Of note, Miaskowski et al.,(14) using a newer method of longitudinal data analysis, reported marked individual variability in fatigue severity during and after RT for prostate cancer.

Most of the studies of symptom trajectories in patients with prostate cancer have evaluated the dimensions of occurrence or severity. However, an

important dimension of the symptom experience is distress.(16) To date, only six studies have reported on the trajectories of distress over the course of RT in patients with prostate cancer.(6, 7, 10, 17-19) All of these studies evaluated distress associated only with urinary, bowel, and/or sexual symptoms. Litwin et al. (7) reported RT-associated bother as it relates to other treatment modalities. In the study by Gore et al.,(18) patients' ratings of distress associated with urinary, bowel, and bladder dysfunction decreased over 48 months. Fransson (17) found no between group differences in urinary bother in a study that compared patients who underwent RT to healthy controls at 15 years post treatment. Schapira et al. (10) found no significant change in urinary or sexual bother from baseline to 12 months after treatment. Krahn et al. (6) found that urinary and bowel bother significantly increased 2 months after treatment and remained elevated at one year post-treatment. In contrast, Namiki et al. (19) reported an increase in urinary bother at one month post RT that had returned to baseline levels at 2 months. Although not a direct measure of symptom distress, it is interesting that Yoshimura et al.(9) found no significant change in "overall satisfaction" with sexual function from baseline to two years after RT despite a significant decrease in sexual function. However, after two years, a significant decrease in overall satisfaction as well as function was reported.

An evaluation of potential predictors of the trajectories of symptoms in prostate cancer patients undergoing RT is an additional way to focus on individual patient outcomes. For example, Chen, Clark, and Talcott (20) found that functional status prior to treatment was positively correlated with quality of

life after surgery or RT. Geinitz et al. (11) found that a higher number of concomitant diseases and having no children were independently predictive of lower global quality of life two years after treatment.

Five additional studies evaluated predictors for specific symptoms in patients with prostate cancer who underwent RT.(14, 18, 19, 21, 22) Miaskowski et al. (14) found that younger age and higher levels of fatigue and depression prior to RT predicted higher levels of morning and/or evening fatigue during and after RT. Thomas et al. (21) found that poorer coping mechanisms were associated with higher levels of sleep disturbance over the course of RT. In their comparison of U.S. and Japanese men who underwent RT for prostate cancer, Namiki et al. (19) found that time since treatment and baseline urinary function and bother scores, but not nationality, were independently associated with improved urinary bother scores at 24 months post treatment. However, nationality was predictive of the slope of recovery for urinary function and bother for these patients. The trajectory was flat in the Japanese cohort and worsened somewhat in the U. S. cohort. Similarly, Gore et al. (18) found that worse urinary, bowel, and sexual function scores through 48 months post treatment for prostate cancer were predictive of severe bother in these domains. In addition, time since treatment was inversely associated with urinary and bowel bother early in treatment but this relationship was no longer noted 48 months post treatment. In their analysis of how neoadjuvant hormonal therapy affected bowel symptoms over the course of RT, Tsai et al. (22) found that men who received hormonal therapy had less rectal pain and tenesmus but more rectal mucus compared to

those who did not. To our knowledge, no study has evaluated multiple predictors for their effects on changes in the multiple dimensions of the symptom experience during and after RT for prostate cancer.

In an effort to orient research more closely to individual patient's experiences, the purpose of this study was to evaluate the trajectories of occurrence, severity, and distress for the six most prevalent symptoms reported by prostate cancer patients undergoing RT and evaluate the effects of selected demographic (i.e., ethnicity) and clinical (i.e., Karnofsky Performance Status (KPS) score, use of hormonal therapy prior to RT, presence of pain at the initiation of RT) characteristics on these trajectories.

METHODS

Patients and settings

This descriptive, longitudinal study is part of a larger study that evaluated the trajectories of multiple symptoms over the course of RT in outpatients with prostate cancer (*n*=82). Patients were recruited from two RT departments located in a Comprehensive Cancer Center and a community-based oncology program at the time of the patient's simulation visit.

Patients were eligible to participate if they were ≥18 years of age; were scheduled to receive primary or adjuvant RT for prostate cancer; were able to read, write, and understand English; gave written informed consent; and had a KPS score of ≥ 60. Patients were excluded if they had: metastatic disease, more than one cancer diagnosis, or a diagnosed sleep disorder.

Instruments

Patients completed a demographic questionnaire, the KPS scale, and the Memorial Symptom Assessment Scale (MSAS). The demographic questionnaire provided information about age, marital status, education, ethnicity, employment status, and the presence of a number of co-morbid conditions. The KPS is commonly used in the assessment of the functional status of cancer patients and has well-established reliability and validity.(23)

The MSAS is a self-report questionnaire designed to measure the multidimensional experience of symptoms and has well-established reliability and validity.(24, 25) It consists of a list of 32 physical and psychological symptoms that occur as a result of cancer or cancer treatment. Patients were asked to use the MSAS to systematically report whether or not they had experienced each of the symptoms in the past week (i.e. symptom occurrence). If the symptom was present, they were asked to rate its frequency, severity, and associated distress. Symptom frequency was measured using a four-point Likert scale (i.e., 1=rarely, 2=occasionally, 3=frequently, 4=almost constantly). Symptom severity was measured using a four-point Likert scale (i.e., 1=slight, 2=moderate, 3=severe, 4=very severe). Symptom distress was measured using a five-point Likert scale (i.e., 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much).

Study procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and at the second site. At the time of the simulation visit (approximately 1 week prior to the initiation of RT), patients were approached by a research nurse to discuss participation in the study. After

obtaining written informed consent (i.e., baseline assessment), they were asked to complete the demographic questionnaire, the KPS, and the MSAS. Additional MSAS assessments were done every other week during the course of RT, every 2 weeks for 2 months, and once a month for 2 months following RT. Most patients completed 11 assessments. At the beginning and end of the study, medical records were reviewed for disease and treatment information.

Data analysis

Data were analyzed using SPSS version 18.0 and Stata version 11.1. Descriptive statistics were used to characterize the sample and to determine the occurrence rates for the six most prevalent symptoms. As shown in Table 1, the occurrence rates for the 32 MSAS symptoms were evaluated at the middle, end, and one month after the completion of RT. The six symptoms that occurred in ≥ 40% of the patients at one or more time points (i.e., problems with urination, pain, lack of energy, feeling drowsy, difficulty sleeping, and diarrhea) were evaluated in the subsequent longitudinal analyses.

Using multilevel generalized linear models, these six symptoms were evaluated for changes over time in symptom occurrence, severity, and distress (i.e. a total of 11 assessments over 6 months). Symptom occurrence was coded as a binary variable (yes=1, no=0) and examined with multilevel logistic regression. Symptom severity items were coded as ordinal with 0=not present and with increasing severity reported as 1 to 4. Symptom distress was coded as ordinal with 0=not present, 1=present but causing no distress, and with increasing distress reported as 2 to 5. Therefore, changes in symptom severity

and distress were examined with multilevel proportional odds ordinal logistic regression [also called cumulative odds logistic regression.(26-30)

For both types of models, random intercepts were estimated with the first assessment being treated as the baseline (or intercept) for the growth trajectory. Unconditional models were examined first to estimate the linear change in the symptom reports. Given the possibility that the growth trajectory might not be only linear, quadratic effects were examined. Further, the treatment period and a lengthy follow-up invited the examination of shifts (also called “discontinuities” (31)) in the growth trajectories. Therefore, piecewise models were examined. Three growth periods were examined with piecewise models: baseline to six weeks, six weeks to 17 weeks (two months after RT); and 17 weeks to 25 weeks (four months after RT).

After identifying the best fitting growth trajectory for each symptom, conditional models were fit to examine the associations for each of four covariates (i.e., ethnicity, KPS score, use of hormonal therapy prior to RT, and presence of pain at the initiation of RT) on the reported symptoms at baseline and on the change in symptoms over time (cross-level interaction). These covariates were examined separately for each symptom.

The multilevel logistic regression models were estimated with Stata release 11.1 (program xtlogit) using mean and variance adaptive Gauss-Hermite quadrature with 12 integration points. The multilevel ordinal regression models were fit in Stata with *gllamm,(30)* a program written for Stata. For these models, estimation was carried out with an ologit link and using adaptive Gauss-Hermite

quadrature with 15 integration points. For both types of multilevel generalized linear models, estimation with adaptive quadrature was shown to be better than pseudo-likelihood estimation,(30) as used in SPSS Version 19, HLM Version 6, and other programs. For all analyses, p-values of < 0.05 were considered statistically significant.

Results

Demographic and Clinical Characteristics of the Sample

The demographic, disease, and treatment characteristics of the 82 patients are presented in Table 2. These men with prostate cancer were approximately 67 years of age, and well educated, and had a KPS score of 95.7. Most of the patients were married or partnered (71.9%), white (76.8%), and not employed (54.4%). The distribution of clinical stage was 48.8% with T1, 42.5% with T2, and 8.8% with T3. Over 50% of the patients had received hormonal therapy prior to the initiation of RT and 47.6% reported pain at the initiation of RT.

Problems with Urination

The likelihood of reporting problems with urination increased from baseline to six weeks (P1), decreased from 6 to 17 weeks (P2), and then remained stable from 17 to 25 weeks (P3; Table 3, Figure 1A). KPS score and the presence of pain at the initiation of RT influenced the occurrence of this symptom at baseline. For each 10 point decrease in KPS score, the odds of reporting problems with urination at the initiation of RT were 2.9 times greater. Patients who reported pain were 14.8 times more likely to report problems with urination at the initiation of

RT. In addition, cross level interactions were found between both ethnicity and pain and changes over time in the odds of reporting problems with urination (see Table 3). As shown in Figures 2A and B, the probability of reporting problems with urination increased more for non-whites than whites from baseline to 6 weeks (P1). As shown in Figures 2C and D, given that these patients started with a higher likelihood of reporting problems with urination at baseline compared to patients without pain, the odds of reporting this symptom increased at a lesser rate in the patients with pain from baseline to 6 weeks (P1), then decreased at a lesser rate from 6 to 17 weeks (P2).

Changes in overall severity ratings for problems with urination were nonlinear, first increasing sharply from baseline to six weeks, then decreasing sharply from six to 17 weeks, then increasing at a lower rate from 17 to 25 weeks (Table 4, Figure 3A). KPS score influenced the severity rating of this symptom at baseline. For each 10 point decrease in KPS score, the odds of reporting a higher severity rating for problems with urination at the initiation of RT were 2.7 times greater. Presence of pain at the initiation of RT was the only predictor that influenced both the severity of this symptom at baseline as well as changes over time in the severity of this symptom. As shown in Table 4 and Figure 4A and B, compared to patients without pain, patients with pain reported more severe problems with urination at baseline. However, the severity of their problems with urination increased at a lesser rate to six weeks, and then decreased less than those with no pain from six to 17, and from 17 to 25 weeks. Differences between the two pain groups were not significant for the second and third “pieces” of the

model. As can be seen in Table 4, the odds of reporting more severe problems with urination at baseline were 6.2 times greater for the patients with pain. Given that they started with more severe problems with urination at baseline, the odds of reporting more severe problems for each additional week were 27% less over the first “piece” of their trajectory for the patients with pain ((OR – 1)*100 = (.73 - 1)*100 = -27%).

Changes in overall distress ratings for problems with urination were nonlinear, first increasing sharply from baseline to six weeks, then decreasing sharply from six to 17 weeks, then remaining stable from 17 to 25 weeks (Table 5, Figure 5A). KPS score was the only predictor that influenced the distress rating for this symptom at baseline. For each 10 point decrease in KPS score, the odds of reporting a higher distress rating for problems with urination at the initiation of RT were 2.7 times greater. Presence of pain influenced changes over time in the distress rating for this symptom. As shown in Table 5 and Figures 6A and B, patients with pain reported that their distress associated with problems with urination increased as a lesser rate from baseline to six weeks, and then decreased less than those with no pain from six to 17, and from 17 to 25 weeks. However, the differences between the two pain groups were not significant for the second and third “pieces” of the model. As can be seen in Table 5, given that patients with pain started with more distress associated with problems with urination at baseline, the odds of reporting higher levels of distress for each additional week were 21% less over the first “piece” for the patients with pain.

Pain

Pain occurrence rates decreased over time (Table 3, Figure 1B). For each additional week, the odds of a patient reporting pain decreased by 4%. Ethnicity, KPS score, and hormonal treatment prior to RT had no effect on the occurrence of pain at baseline or changes in its occurrence over time (Table 3). Severity (Figure 3B) and distress (Figure 5B) ratings for pain decreased over time. For each additional week, the odds of a patient reporting a higher pain severity (Table 4) or distress (Table 5) score decreased by 5% for both dimensions. None of the predictors had an effect on severity or distress scores.

Lack of energy

Occurrence rates for lack of energy decreased over time (Table 3, Figure 1C). For each additional week, the odds of a patient reporting lack of energy decreased by 6%. Ethnicity, KPS score, and hormonal treatment prior to RT had no effect on the occurrence of lack of energy at baseline (Table 3). However, patients who reported pain were 6.9 times more likely to report lack of energy at the initiation of RT. In addition, cross level interactions were found between both hormonal treatment and pain prior to RT and changes over time in the odds of reporting lack of energy. As shown in Table 3 and Figures 7A and B, for each additional week, the odds of reporting lack of energy increased by 6% in patients who had hormonal treatment prior to RT. As shown in Table 3 and Figures 7C and D, for each additional week, the odds of reporting lack of energy decreased by 9% in patients who reported pain.

Changes in the overall severity ratings for lack of energy followed a decreasing linear trajectory over the 25 weeks, with an approximate 6%

decrease in the odds of reporting higher severity ratings for lack of energy with each additional week (Table 4, Figure 3C). KPS score was the only predictor that influenced the severity rating for this symptom at baseline. For each 10 point decrease in KPS score, the odds of reporting a higher severity rating for lack of energy at the initiation of RT were 2.7 times greater. Presence of pain influenced changes over time in the severity rating for this symptom. As shown in Table 4 and Figures 8A and B, patients with pain started higher and reported a sharper decrease (7%) in the odds of reporting higher severity ratings for lack of energy, compared to patients without pain.

Changes in the overall distress ratings for lack of energy followed a decreasing linear trajectory over the 25 weeks, with an approximate 4% decrease in the odds of reporting higher distress ratings for lack of energy with each additional week (Table 5, Figure 5C). KPS score was the only predictor that influenced the distress rating for this symptom at baseline. For each 10 point decrease in KPS score, the odds of reporting a higher distress rating for lack of energy at the initiation of RT were 2.7 times greater. Hormonal treatment and presence of pain influenced changes over time in the distress ratings for this symptom. As shown in Table 5 and Figures 9A and B, for each additional week, the probability of reporting a higher distress score for lack of energy increased by 5% in patients who had hormonal treatment prior to RT. As shown in Table 5 and Figures 9C and D, patients with pain started higher and reported a sharper decrease (7%) in the odds of reporting higher distress ratings for lack of energy, compared to patients without pain.

Feeling drowsy

Occurrence rates for feeling drowsy decreased over time (Table 3, Figure 1D). For each additional week, the odds of a patient reporting feeling drowsy decreased by 5%. Only KPS score influenced the occurrence of this symptom at baseline. For each 10 point decrease in KPS score, the odds of reporting feeling drowsy at the initiation of RT were 3.1 times greater. Severity (Figure 3D) and distress (Figure 5D) ratings for feeling drowsy decreased over time. For each additional week, the odds of a patient reporting a higher severity (Table 4) or distress (Table 5) score for feeling drowsy decreased by 3% for both dimensions. KPS score was the only predictor associated with baseline severity and distress ratings for this symptom. For each 10 point decrease in KPS score, the odds of reporting higher severity and distress ratings for feeling drowsy at the initiation of RT were 3.4 and 3.5 times greater, respectively.

Difficulty sleeping

Occurrence rates for difficulty sleeping decreased over time (Table 3, Figure 1D). For each additional week, the odds of a patient reporting difficulty sleeping decreased by 5%. Only KPS score influenced the occurrence of this symptom at baseline. For each 10 point decrease in KPS score, the odds of reporting difficulty sleeping at the initiation of RT were 7.5 times greater.

Severity (Figure 3E) and distress (Figure 5E) ratings for difficulty sleeping decreased over time. For each additional week, the odds of a patient reporting a higher severity (Table 4) or distress (Table 5) score for difficulty sleeping decreased by 5% and 4%, respectively. KPS score was the only predictor

associated with baseline severity and distress ratings for this symptom. For each 10 point decrease in KPS score, the odds of reporting higher severity and distress ratings for difficulty sleeping at the initiation of RT were 7.5 and 7.0 times greater, respectively.

Diarrhea

The likelihood of reporting diarrhea increased from baseline to six weeks (P1), decreased from 6 to 17 weeks (P2), and then increased from 17 to 25 weeks (P3; Table 3, Figure 1F). KPS score influenced the occurrence of this symptom at baseline. For each 10 point decrease in KPS score, the odds of reporting diarrhea at the initiation of RT were 3.1 times greater.

Changes in severity (Table 4, Figure 3F) and distress ratings (Table 5, Figure 5F) for diarrhea were nonlinear, first increasing sharply from baseline to six weeks, then decreasing sharply from six to 17 weeks, then increasing at a lower rate from 17 to 25 weeks. While significant for distress, the slight increase in severity from 17 to 25 weeks was not statistically significant. KPS score was the only predictor associated with baseline severity and distress ratings for this symptom. For each 10-point decrease in KPS score, the odds of reporting higher severity and distress ratings for diarrhea at the initiation of RT were 3.0 and 2.9 times greater, respectively.

DISCUSSION

This study is the first to examine changes in multiple dimensions of the symptom experience (i.e., occurrence, severity, and distress) for six of the most common symptoms reported by patients prior to, during, and following RT for prostate cancer. While genitourinary and gastrointestinal symptoms were reported by ≥ 40% of these patients, four additional symptoms (i.e. pain, lack of energy, feeling drowsy, difficulty sleeping) emerged as significant clinical problems for these men with prostate cancer that are highly prevalent and have not been well studied. Although fatigue is known to be a significant symptom during RT,(32-34) the potentially associated symptoms of feeling drowsy and difficulty sleeping are equally common, severe, and distressing to patients with prostate cancer during and after RT. These two symptoms may be more amenable to targeted intervention than fatigue. The finding of a relatively high prevalence of pain in these patients early in the course RT is important. The source of pain in these men was not established but the fact that nearly half of them reported its presence highlights the need for a thorough pain assessment and ongoing treatment throughout therapy.

An evaluation of the trajectories for occurrence, severity, and distress for all six of the most common symptoms demonstrated that patient's ratings for all three dimensions followed similar trends. Problems with urination and diarrhea were the only exceptions. Between weeks 17 and 25, occurrence and distress ratings related to problems with urination remained constant while severity ratings increased. The general trend for problems with urination (I.e., an increase

after treatment initiation with a subsequent decline) mirrors findings from previous studies.(5, 7, 8) The subtle finding, that distress related to problems with urination is correlated with occurrence rather than severity suggests that continued emotional support, even after treatment ends, is warranted, at least as long as symptoms persist.

Consistent with previous reports,(6, 13) diarrhea increased in frequency during treatment and subsequently decreased, with similar trajectories for ratings of severity and distress. However, the use of piecewise modeling revealed that this particular cohort reported a delayed lesser yet significant increase in the symptom, between 17 and 25 weeks after treatment. The reason for this increase in diarrhea is unclear. One explanation may be that patients received more frequent follow-up and better symptom management for up to 17 weeks after treatment. An equally plausible explanation is that patients may have adhered to special diets until roughly that time. Generally speaking, it is proposed that as time since treatment lengthens and usual lifestyles resume, chronic side effects become more apparent. This new finding, that all three dimensions of this symptom had a delayed significant increase is important because it changes the expected trajectory of treatment related diarrhea and provides evidence that patients need more long-term symptom management support.

For all three dimensions, the trajectories of the other four symptoms studied (i.e. pain, lack of energy, feeling drowsy, difficulty sleeping) followed a similar pattern. Occurrence, severity, and distress were highest at baseline and decreased by roughly 5% with each additional week. No other study has reported

a steady downward pain trajectory. Results of previous studies suggest that pain remains stable, increases, or varies depending on the type of RT received.(6, 12, 13) The reason that pain decreased over time in this study is unclear.

Despite the fact that fatigue is known to be one of the most common and significant symptoms associated with RT, in this study, for all of the symptom dimensions the trajectories of lack of energy, feeling drowsy, and difficulty sleeping steadily improved over the course of treatment. Thomas et al. (21) found the equally puzzling result that despite reporting fewer hours of sleep through six months after treatment all other measures of sleep (e.g. trouble falling asleep, sleep adequacy, sleep latency) improved or remained constant over time. Taken together, these findings suggest the need for additional research on these symptoms.

Several studies found that functional status prior to RT impacts symptom trajectories over the course of treatment for prostate cancer.(8, 18, 20) The majority of research focused on how functional status affects urinary, bowel, and sexual function. No studies were found that evaluated the impact of functional status on other RT-related symptoms. In this study, the odds of reporting problems with urination, diarrhea, feeling drowsy, and difficulty sleeping at the beginning of treatment steadily increased as KPS score decreased. Interestingly, no association was found between the occurrence of pretreatment lack of energy and KPS score. Of note, baseline symptom severity and distress did have an inverse relationship with KPS score for all symptoms except pain. It is not entirely

clear why KPS score only affected the baseline dimension of each of the symptoms but not the trajectories of the various symptoms.

Ethnicity was found to have a significant interaction with only the occurrence of problems with urination between baseline and 6 weeks. Nonwhite patients were more likely than white patients to report an increase in problems with urination during this time. The reason for this finding is not entirely clear.

It is interesting that none of the predictors evaluated affected any dimension of pain at baseline or the trajectories of pain. In contrast, pretreatment pain was predictive of occurrence of lack of energy, and occurrence and severity of problems with urination at baseline. It did not affect symptom related distress before treatment. In contrast, a lower KPS score was predictive of increased severity and distress related to lack of energy at baseline but did not affect its occurrence. Those patients with pretreatment pain experienced more rapid improvement in energy level over time, and a less marked peak in problems with urination during treatment. These findings suggest that pain is not necessarily related to performance status and that better pain management, especially at the onset of treatment, may have a positive effect on symptom trajectories. Blesch et al. (35) found that pain was highly correlated with fatigue in cancer patients but the relationship between pain and other symptoms in prostate cancer patients undergoing RT is virtually unexplored, and warrants further exploration.

Consistent with previous reports,(11, 22) no interactions were found between hormonal treatment prior to RT and problems with urination or diarrhea. However, patients who received hormonal treatment prior to RT were more likely

to report occurrence of and distress related to lack of energy over time than those who had not received hormonal treatment. This information can be used to educate patients about risk factors for fatigue. In addition, it is interesting that distress level followed the same trajectory as occurrence rather than severity. This finding suggests that any complaint of lack of energy should be taken seriously, regardless of severity.

It is notable that patients in this study did not report their symptoms to be more than moderately severe. Furthermore, for all time points, with the exception of problems with urination, the greatest likelihood that patients would report even slight symptom severity or mild symptom distress was only approximately 50% or 40%, respectively. These findings suggest, that during and after RT, clinicians must listen carefully for reports of difficulty with symptom management because patients with prostate cancer are not likely to rate their symptoms as severe or very distressing.

Many studies have explored the effects of RT on sexual function in patients with prostate cancer. In this study, problems with sexual interest or activity were not found to be one of the most common symptoms. One explanation for this finding is that perhaps not all patients were sexually active. This finding is important because it suggests that a greater number of patients would benefit from future research on symptoms that are more common and not as well characterized (e.g., pain, feeling irritable).

Limitations of this study include the relatively small sample size and high proportion of white patients. Future studies that include more ethnically diverse

samples are needed to further explore the relationship between ethnicity and symptom trajectories. Because patients in this study had an initial KPS score of ≥ 60 and no metastatic disease, its results cannot be generalized to prostate cancer patients with lower functional status or more extensive disease. Although the trajectories of multiple dimensions of pain were evaluated, as well as how its presence at the initiation of RT affected the trajectories of other common symptoms, the causes of pain were not assessed. More detailed information on the causes and nature of pain in this population would be useful in the application of these findings to the clinical setting.

In summary, this study is the first to report on which six symptoms are the most common in men with prostate cancer who underwent RT. In addition, it is the first to simultaneously examine the trajectories of occurrence, severity, and distress for these symptoms. Through an evaluation of how a number of predictors influence these trajectories, we determined that lower KPS score at the initiation of RT leaves one more likely to report, with increased severity and distress, problems with urination, diarrhea, feeling drowsy, and difficulty sleeping at that time. It is remarkable that no predictors for pain were identified, including KPS score. The presence of pretreatment pain was the only predictor of the presence of lack of energy before treatment. This finding suggests that better pain control, regardless of treatment phase, may lead to improvements in fatigue. We were only able to examine the trajectories of the six most frequent symptoms in this population but there are a number of other common symptoms that warrant further attention. For example, it is notable that roughly one third of the

men in this study reported feeling irritable, having difficulty concentrating, and sweats. These symptoms are prime areas for future patient-centered research, and results of this study might be used by others to further prioritize efforts.

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Table 1. Occurrence Rates for Symptoms at the Middle, End, and One Month After the Completion of Radiation Therapy (RT)

MSAS symptom	Middle (%)	End (%)	One Month (%)
Problems with urination	68.4	72.8	62.2
Pain	47.6	39.7	32.4
Lack of energy	45.1	50.0	39.7
Feeling drowsy	42.6	43.6	41.9
Difficulty sleeping	41.3	38.0	42.5
Diarrhea	40.5	28.6	10.8
Feeling irritable	34.2	26.6	32.4
Problems with sexual interest or activity	32.5	34.2	35.2
Sweats	32.1	26.0	24.3
Difficulty concentrating	27.9	24.1	15.1
Constipation	20.0	15.7	12.2
Worrying	19.3	23.9	21.9
Feeling sad	19.1	14.5	19.2
Dry mouth	13.9	13.0	13.5
Feeling nervous	13.8	16.6	12.3
Numbness/tingling in hands/feet	13.0	8.0	12.2
Cough	12.7	15.4	12.2
Itching	12.6	17.2	8.1
Shortness of breath	10.2	6.5	5.4
Lack of appetite	10.1	3.9	4.1
Feeling bloated	8.9	9.1	5.4
Nausea	8.8	6.6	2.7
Dizziness	8.8	10.7	5.4
Weight loss	6.5	5.4	2.7
Change in the way food tastes	6.4	3.9	1.4
Changes in skin	5.6	3.9	4.1
“I don’t look like myself”	3.9	2.8	5.5
Swelling of arms or legs	3.9	2.6	1.4
Mouth sores	2.6	2.6	2.7
Vomiting	1.3	1.3	1.4
Hair loss	1.3	1.3	2.7
Difficulty swallowing	1.3	0	1.4

Table 2. Demographics, Disease, and Treatment Characteristics of Patients with Prostate Cancer (*n*=82)

Characteristic	Mean (SD)
Age (years)	67.1 (7.8)
Education (years)	16.0 (3.2)
Karnofsky Performance Status score	95.6 (6.9)
	% (n)
Married or partnered	71.9 (59)
Lives alone	23.2 (19)
Ethnicity-white	76.8 (63)
Employed	45.6 (36)
Have children at home	11.3 (8)
Have parent at home	1.4 (1)
	Mean (SD)
Height (inches)	70.5 (2.7)
Weight at assessment 1 (pounds)	195.2 (30.6)
Pre-treatment PSA level (nanograms/milliliter)	10.2(8)
Gleason score (Mean (SD))	6.8(0.9)
Total dose of RT prescribed (cGys)	6840.7 (1031.6)
Total daily dose of RT (cGys)	184.4 (8.4)
	% (n)
Gleason score	
5 or 6	39.5 (32)
7	46.9 (38)
≥8	13.6 (11)
Clinical stage	
T1	48.8 (39)
T2	42.5 (34)
T3	8.8 (7)
Prostatectomy prior to RT	9.8 (8)
Hormonal therapy prior to RT	52.5 (42)
RT treatment plan	
Whole pelvis + conformal	9.8 (8)
Whole pelvis + conformal boost	75.6 (62)
Whole pelvis + high dose RT	4.9 (4)
Whole pelvis + permanent seed implant	9.8 (8)

cGys=centigrays, PSA=prostate specific antigen, RT=radiation therapy, SD=standard deviation

Table 3 – Results of the multilevel regression analyses of occurrence ratings for six symptoms reported by patients with prostate cancer over 25 weeks

PROBLEMS WITH URINATION - OCCURRENCE								
Variables	Unconditional Model				Conditional Model			
	OR	SE[a]	CI	p-value	OR	SE	CI	p-value
Piecewise model								
P1-significant increase	1.83	0.15	1.56-2.15	<0.0001				
P2-significant decrease	0.42	0.05	0.33-0.53	<0.0001				
P3-not significant	1.15	0.08	0.99-1.32	0.063				
Ethnicity								
At baseline					Not significant			
P1 weeks – significant increase					2.49	0.45	1.75-3.56	<0.0001
P2 weeks – significant decrease					0.30	0.08	0.18-0.51	<0.0001
P3 weeks – not significant					Not significant			
P1 – Cross level interaction					0.67	0.13	0.45-0.996	0.048
P2 – Cross level interaction					Not significant			
P3 – Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					2.87	1.45	1.07-7.74	0.037
Cross level interactions					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					14.77	15.59	1.87-116.91	0.011
P1 weeks – significant increase					2.05	0.20	1.70-2.48	<0.0001
P2 weeks – significant decrease					0.37	0.05	0.28-0.48	<0.0001
P3 weeks – significant increase					1.20	0.10	1.02-1.42	0.029
P1 – Cross level interaction					0.65	0.12	0.46-0.92	0.016
P2 – Cross level interaction					1.70	0.45	1.02-2.84	0.044
P3 – Cross level interaction					Not significant			
PAIN - OCCURRENCE								
Decreasing linear	0.96	0.01	0.93-0.98	0.001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					Not significant			
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
LACK OF ENERGY - OCCURRENCE								
Decreasing linear	0.94	0.01	0.92-0.97	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					Not significant			
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Weeks					0.91	0.02	0.88-0.95	<0.0001
Cross level interaction					1.06	0.03	1.01-1.13	0.031
Presence of pain at the initiation of radiation therapy								
At baseline					6.87	5.93	1.26-37.22	0.026
Weeks					0.96	0.15	0.93-0.99	0.016
Cross level interaction					0.91	0.03	0.85-0.98	0.011
FEELING DROWSY – OCCURRENCE								
Decreasing linear	0.95	0.01	0.93-0.98	0.001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					3.06	1.65	1.06-8.82	0.038

Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
DIFFICULTY SLEEPING – OCCURRENCE								
Decreasing linear	0.95	0.01	0.92-0.97	<0.0005				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					7.05	3.31	2.80-17.71	0.001
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
DIARRHEA – OCCURRENCE								
Piecewise model								
P1-significant increase	1.56	0.12	1.34-1.81	<0.0001				
P2-significant decrease	0.45	0.05	0.36-0.56	<0.0001				
P3-significant increase	1.52	0.13	1.28-1.79	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interactions					Not significant			
Karnofsky Performance Status score								
At baseline					3.09	1.27	1.38-6.90	0.006
Cross level interactions					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			

[a]Standard errors are for the coefficients on the log scale, not for the odds ratios.

Table 4 – Results of the multilevel regression analyses of severity ratings for six symptoms reported by patients with prostate cancer over 25 weeks

PROBLEMS WITH URINATION - SEVERITY								
Variables	Unconditional Model				Conditional Model			
	OR	SE[a]	CI	p-value	OR	SE	CI	p-value
Piecewise model								
P1-significant increase	1.83	0.12	1.61-2.09	<0.0001				
P2-significant decrease	0.41	0.04	0.34-0.50	<0.0001				
P3-significant increase	1.16	0.07	1.03-1.30	0.016				
Ethnicity								
At baseline					Not significant			
Cross level interactions					Not significant			
Karnofsky Performance Status score								
At baseline					2.68	1.28	1.05-6.86	0.039
Cross level interactions					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					6.24	5.72	1.03-37.64	0.046
P1 weeks – significant increase					2.00	0.16	1.71-2.34	<0.0001
P2 weeks – significant decrease					0.38	0.04	0.30-0.47	<0.0001
P3 weeks – significant increase					1.16	0.08	1.02-1.33	0.029
P1 – Cross level interaction					0.73	0.11	0.55-0.97	0.028
P2 – Cross level interaction					Not significant			
P3 – Cross level interaction					Not significant			
PAIN – SEVERITY								
Decreasing linear	0.95	0.01	0.93-0.98	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					Not significant			
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
LACK OF ENERGY - SEVERITY								
Decreasing linear	0.94	0.01	0.92-0.96	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					2.67	1.26	1.06-6.74	0.038
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Weeks					0.96	0.01	0.93-0.98	0.002
Cross level interaction					0.93	0.03	0.88-0.98	0.013
FEELING DROWSY – SEVERITY								
Decreasing linear	0.97	0.01	0.94-0.99	0.004				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					3.37	1.61	1.32-8.60	0.011
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
Presence of pain at the initiation of radiation therapy								

At baseline					Not significant			
Cross level interaction					Not significant			
DIFFICULTY SLEEPING – SEVERITY								
Decreasing linear	0.95	0.01	0.93-0.97	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					7.49	3.51	2.99-18.75	<0.0001
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
DIARRHEA – SEVERITY								
Piecewise model								
P1-significant increase	1.48	0.10	1.291.70	<0.0001				
P2-significant decrease	0.50	0.05	0.41-0.60	<0.0001				
P3-significant increase	1.41	0.11	1.21-1.65	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interactions					Not significant			
Karnofsky Performance Status score								
At baseline					2.99	1.17	1.39-6.42	0.005
Cross level interactions					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			

[a]Standard errors are for the coefficients on the log scale, not the odds ratios.

Table 5 – Results of the multilevel regression analyses of distress ratings for six symptoms reported by patients with prostate cancer over 25 weeks

PROBLEMS WITH URINATION - DISTRESS								
Variables	Unconditional Model				Conditional Model			
	OR	SE[a]	CI	p-value	OR	SE	CI	p-value
Piecewise model								
P1-significant increase	1.63	0.09	1.46-1.82	<0.0001				
P2-significant decrease	0.51	0.04	0.44-0.59	<0.0001				
P3-not significant	1.08	0.06	0.97-1.20	0.146				
Ethnicity								
At baseline					Not significant			
Cross level interactions					Not significant			
Karnofsky Performance Status score								
At baseline					2.70	1.28	1.07-6.84	0.036
Cross level interactions					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
P1 weeks – significant increase					1.75	0.12	1.53-1.99	<0.0001
P2 weeks – significant decrease					0.47	0.04	0.39-0.56	<0.0001
P3 weeks – not significant					Not significant			
P1 – Cross level interaction					0.79	0.09	0.63-0.999	0.049
P2 – Cross level interaction					Not significant			
P3 – Cross level interaction					Not significant			
PAIN - DISTRESS								
Decreasing linear	0.95	0.01	0.93-0.97	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					Not significant			
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
LACK OF ENERGY - DISTRESS								
Decreasing linear	0.96	0.01	0.94-0.98	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					2.74	1.22	1.14-6.57	0.024
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Weeks					0.94	0.02	0.90-0.97	<0.0001
Cross level interaction					1.05	0.02	1.01-1.10	0.025
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Weeks					Not significant			
Cross level interaction					0.93	0.02	0.89-0.98	0.010
FEELING DROWSY – DISTRESS								
Decreasing linear	0.97	0.01	0.95-0.995	0.016				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					3.46	1.70	1.32-9.09	0.012
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			

Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
DIFFICULTY SLEEPING - DISTRESS								
Decreasing linear	0.96	0.01	0.94-0.98	0.001				
Ethnicity								
At baseline					Not significant			
Cross level interaction					Not significant			
Karnofsky Performance Status score								
At baseline					6.95	3.10	2.90-16.66	<0.0001
Cross level interaction					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Cross level interaction					Not significant			
DIARRHEA - DISTRESS								
Piecewise model								
P1-significant increase	1.51	0.10	1.32-1.73	<0.0001				
P2-significant decrease	0.48	0.05	0.39-0.58	<0.0001				
P3-significant increase	1.46	0.11	1.25-1.70	<0.0001				
Ethnicity								
At baseline					Not significant			
Cross level interactions					Not significant			
Karnofsky Performance Status score								
At baseline					2.92	1.13	1.37-6.25	0.006
Cross level interactions					Not significant			
Hormonal treatment prior to radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			
Presence of pain at the initiation of radiation therapy								
At baseline					Not significant			
Cross level interactions					Not significant			

[a]Standard errors are for the coefficients on the log scale, not the odds ratios.

Figure 1

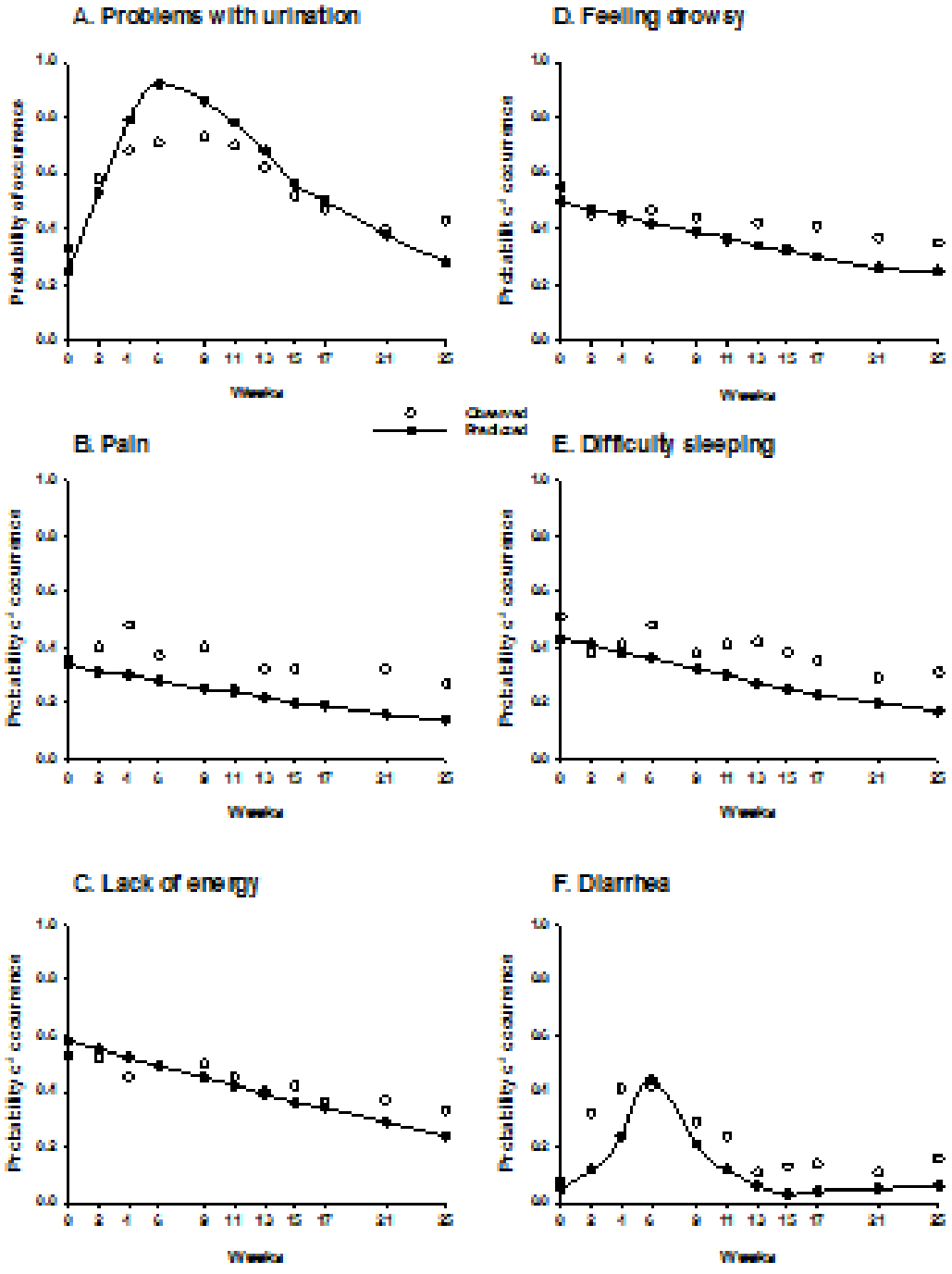

A. Problems with urination
D. Feeling drowsy
B. Pain
E. Difficulty sleeping
C. Lack of energy
F. Diarrhea
Probability of occurrence
Weeks
Observed
Predicted

Figure 2

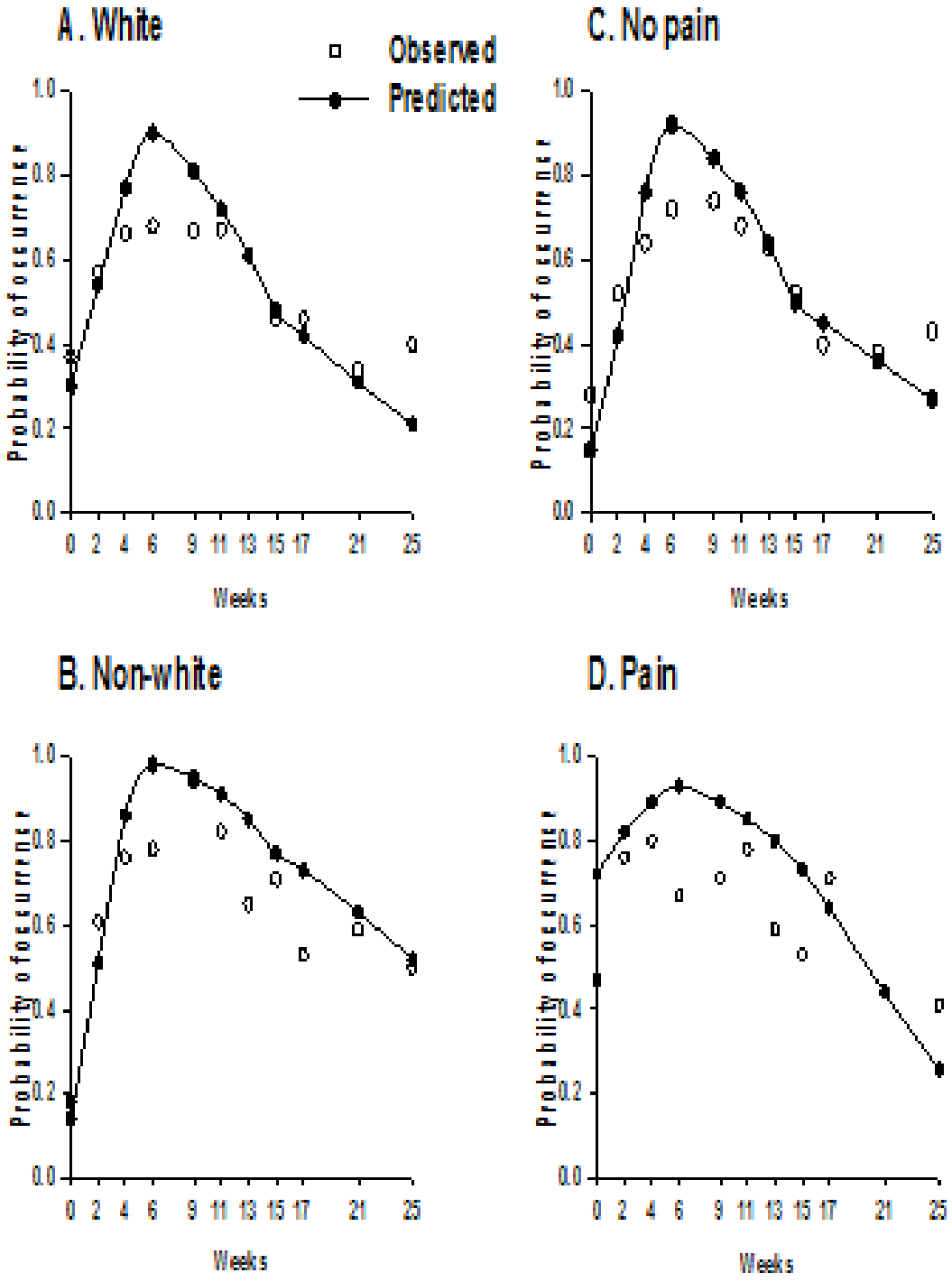

A. White
Observed
Predicted
C. No pain
B. Non-white
D. Pain
Probability of occurrence
Weeks
0.0
0.2
0.4
0.6
0.8
1.0
0 2 4 6 9 11 13 15 17 21 25

Figure 3

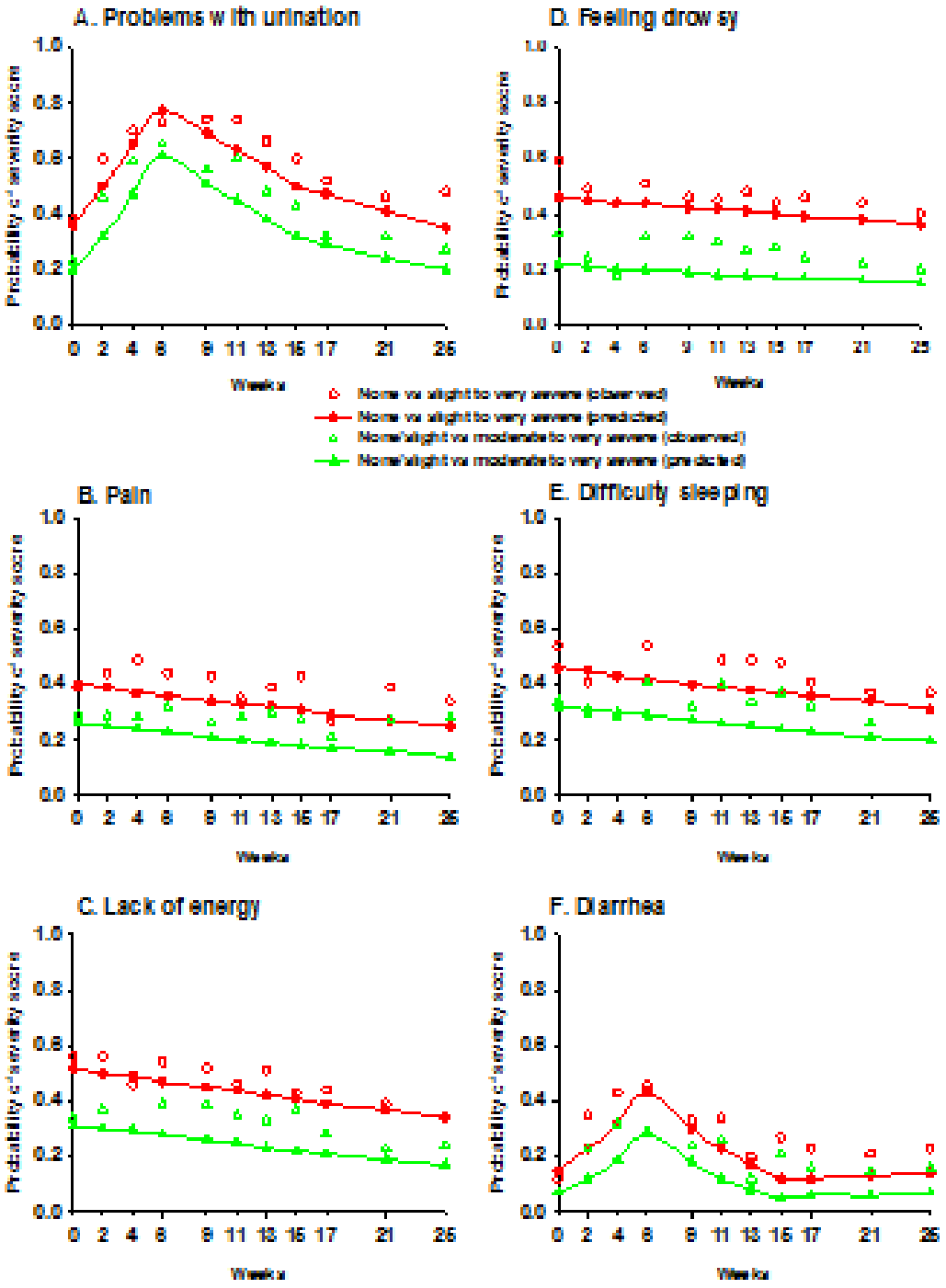

A. Problems with urination
D. Feeling drowsy
B. Pain
E. Difficulty sleeping
C. Lack of energy
F. Diarrhea
Probability of severity score
Weeks
None vs slight to very severe (observed)
None vs slight to very severe (predicted)
None/slight vs moderate to very severe (observed)
None/slight vs moderate to very severe (predicted)

Figure 4

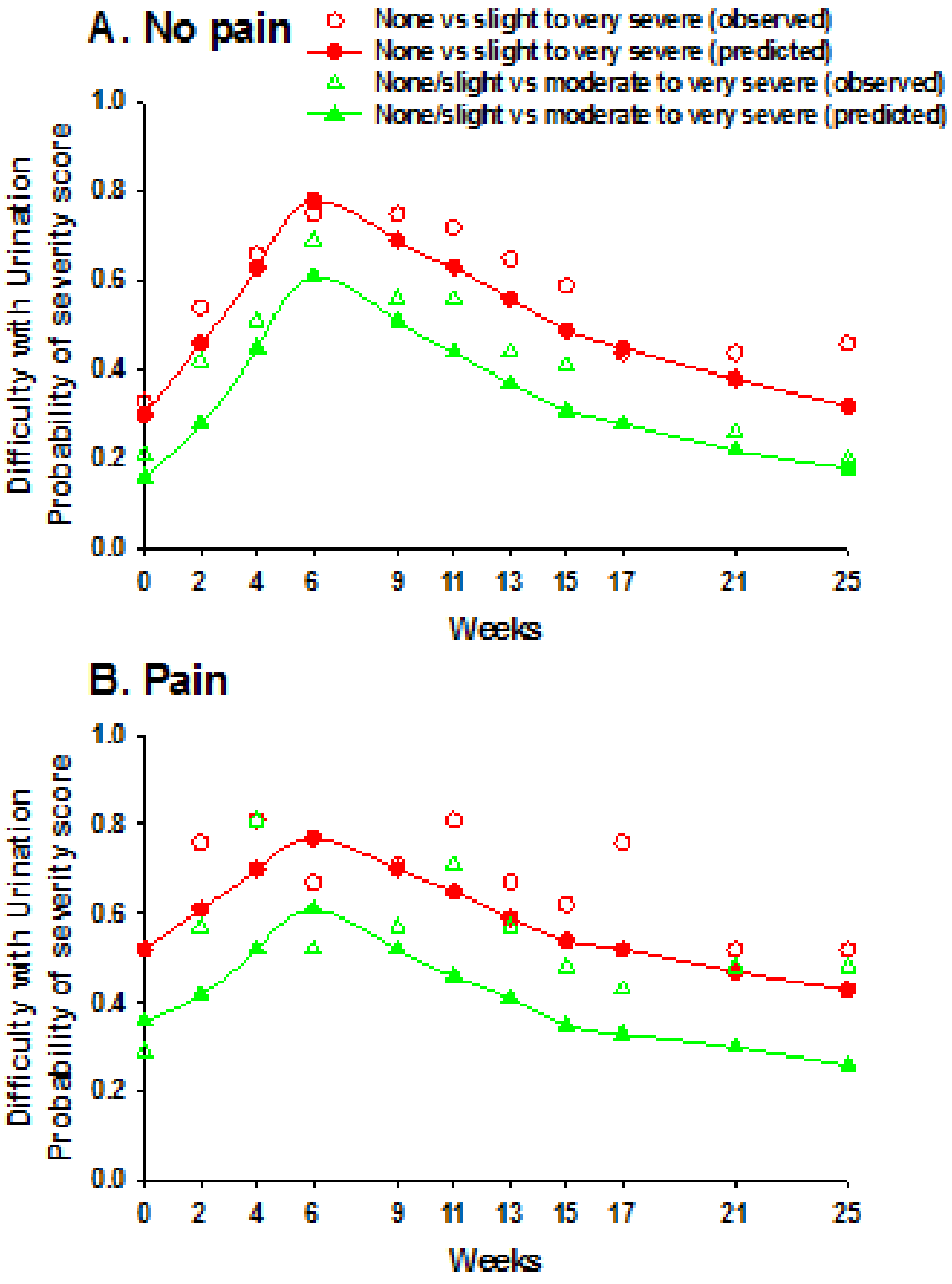

A. No pain
None vs slight to very severe (observed)
None vs slight to very severe (predicted)
None/slight vs moderate to very severe (observed)
None/slight vs moderate to very severe (predicted)
Difficulty with Urination
Probability of severity score
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
9
11
13
15
17
21
25
Weeks
B. Pain
Difficulty with Urination
Probability of severity score
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
9
11
13
15
17
21
25
Weeks

Figure 5

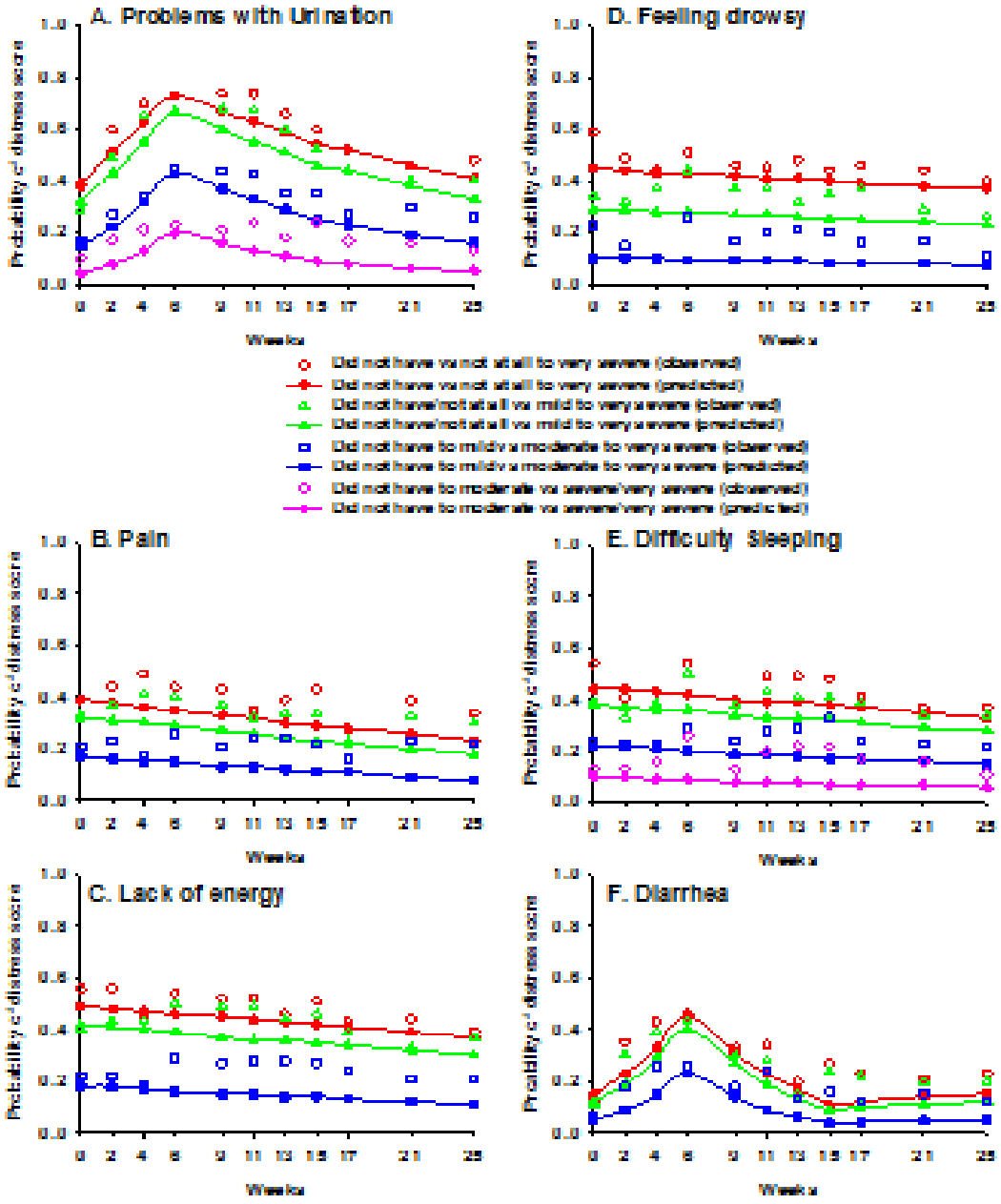

A. Problems with Urination
D. Feeling drowsy
B. Pain
E. Difficulty sleeping
C. Lack of energy
F. Diarrhea
Probability of distress score
Week x
Did not have vs not at all to very severe (observed)
Did not have vs not at all to very severe (predicted)
Did not have/not at all vs mild to very severe (observed)
Did not have/not at all vs mild to very severe (predicted)
Did not have to mild/vs moderate to very severe (observed)
Did not have to mild/vs moderate to very severe (predicted)
Did not have to moderate vs severe/very severe (observed)
Did not have to moderate vs severe/very severe (predicted)

Figure 6

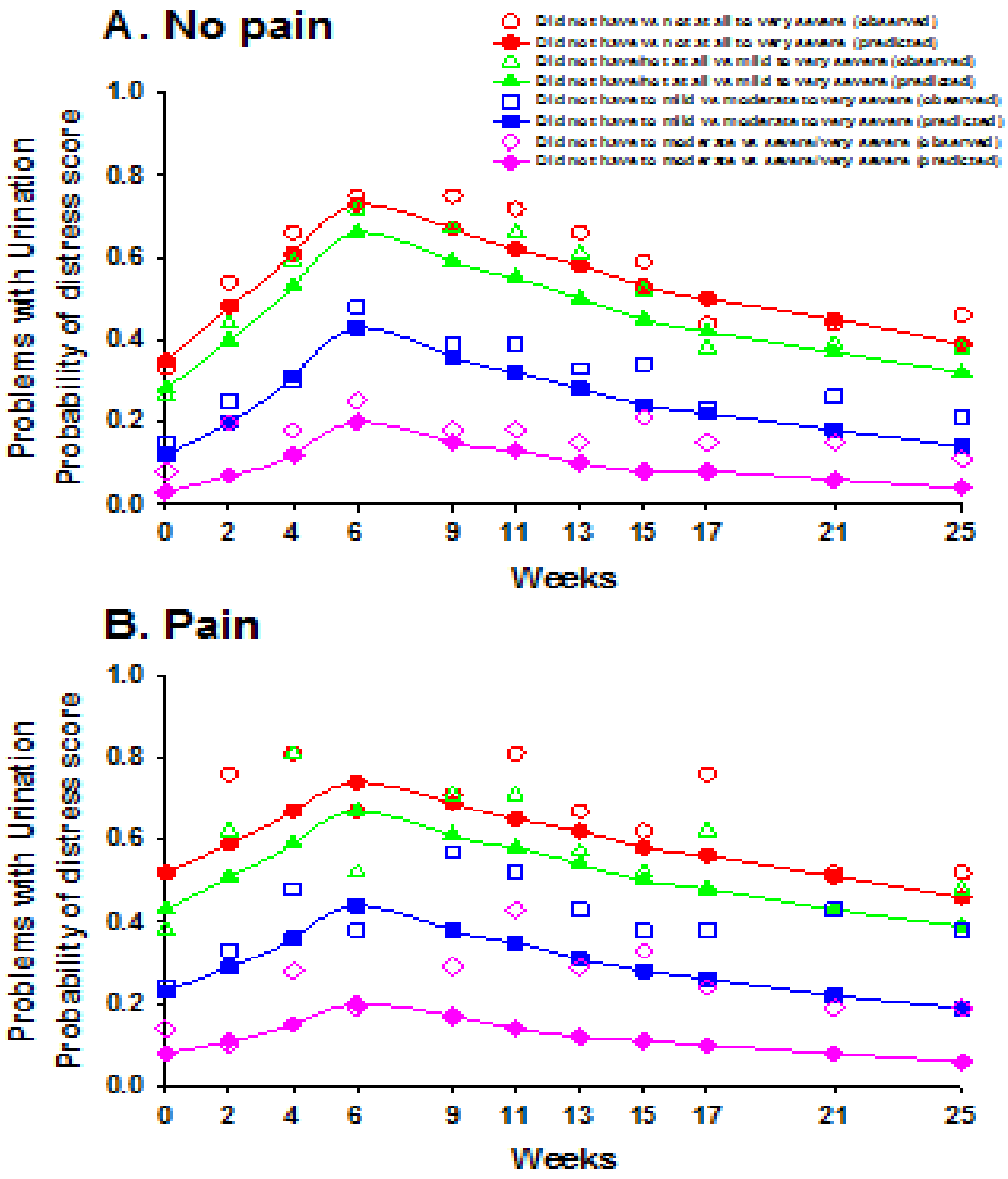

A. No pain
Problems with Urination
Probability of distress score
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
9
11
13
15
17
21
25
Weeks
B. Pain
Problems with Urination
Probability of distress score
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
9
11
13
15
17
21
25
Weeks

Figure 7

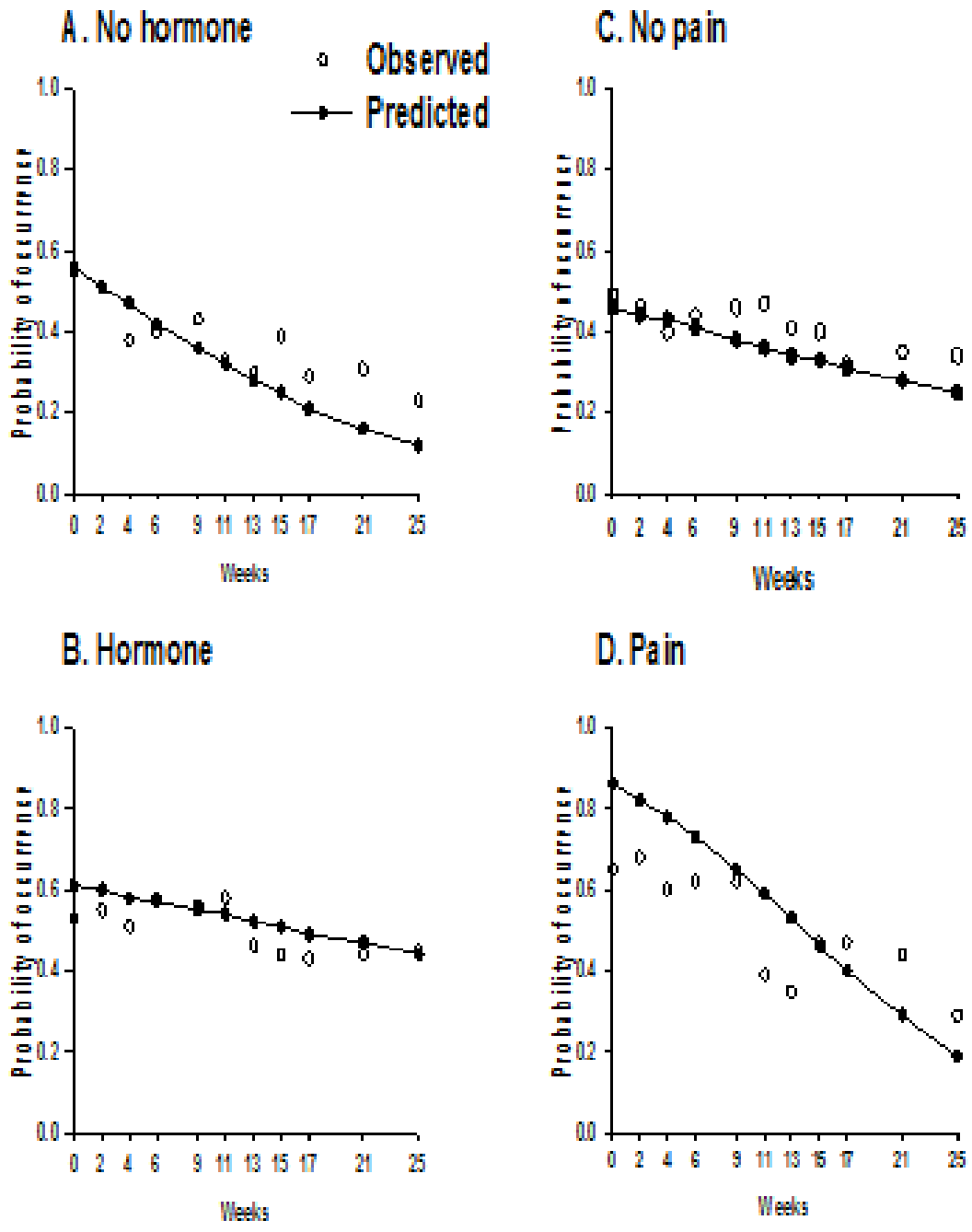

A. No hormone
Observed
Predicted
Probability of occurrence
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 9 11 13 15 17 21 25
Weeks
C. No pain
Probability of occurrence
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 9 11 13 15 17 21 25
Weeks
B. Hormone
Probability of occurrence
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 9 11 13 15 17 21 25
Weeks
D. Pain
Probability of occurrence
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 9 11 13 15 17 21 25
Weeks

Figure 8

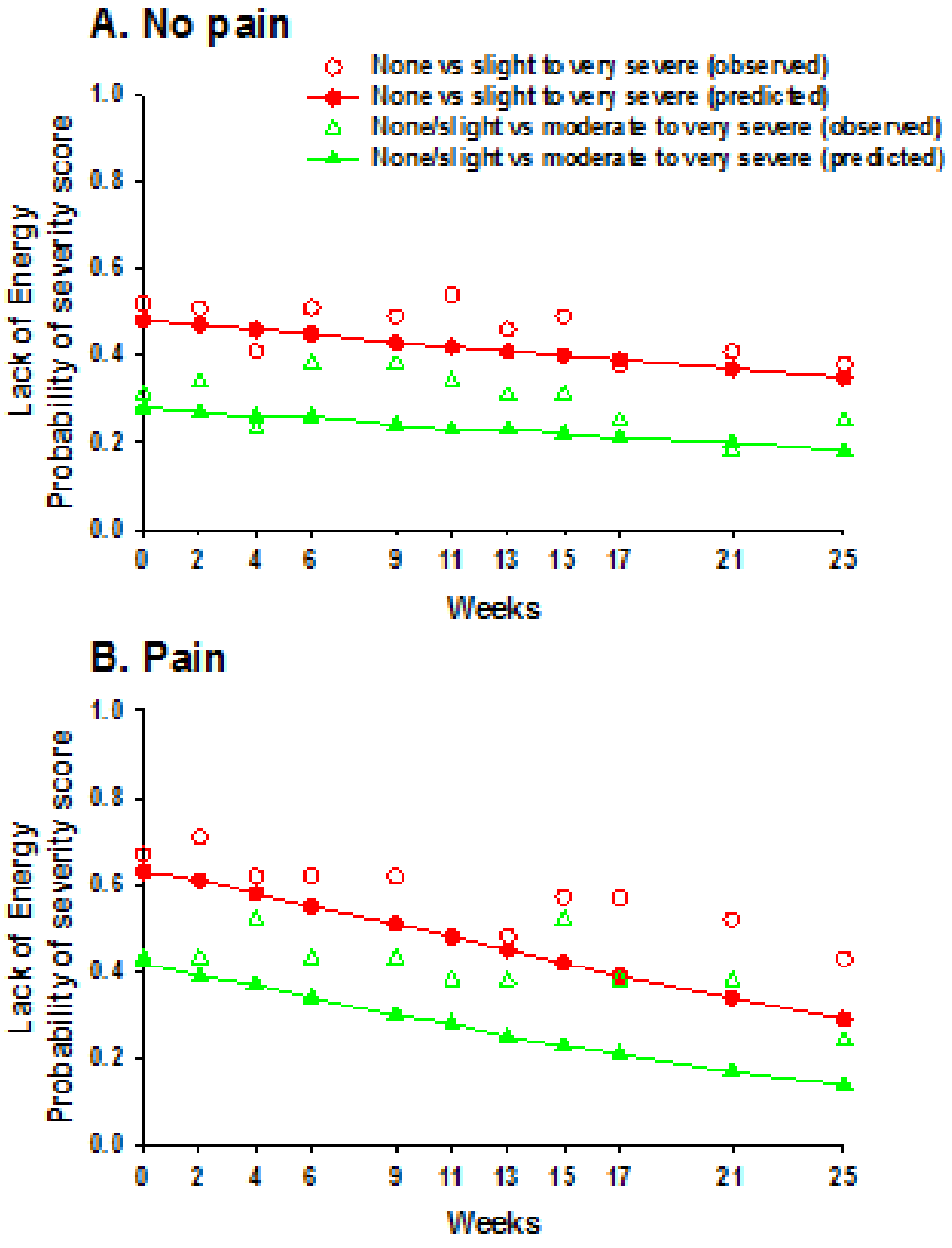
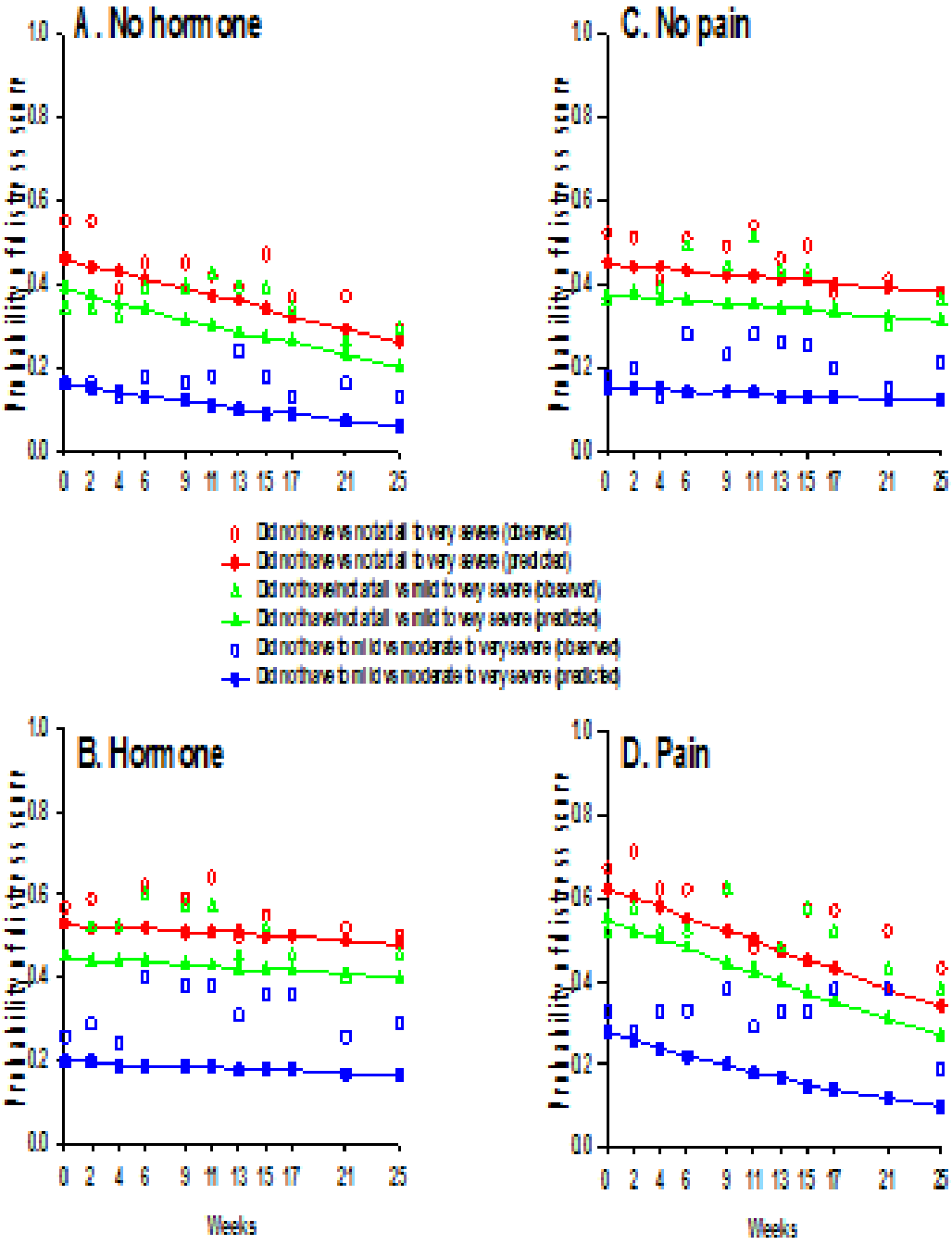

A. No pain
None vs slight to very severe (observed)
None vs slight to very severe (predicted)
None/slight vs moderate to very severe (observed)
None/slight vs moderate to very severe (predicted)
Lack of Energy
Probability of severity score
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
9
11
13
15
17
21
25
Weeks
B. Pain
Lack of Energy
Probability of severity score
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
9
11
13
15
17
21
25
Weeks

Figure 9


A. No hormone
C. No pain
B. Hormone
D. Pain
Probability of distress score
0.0
0.2
0.4
0.6
0.8
1.0
0 2 4 6 9 11 13 15 17 21 25
Weeks
Old mothane vs not at all to very severe (observed)
Old mothane vs not at all to very severe (predicted)
Old mothane not at all vs mild to very severe (observed)
Old mothane not at all vs mild to very severe (predicted)
Old mothane to mild vs moderate to very severe (observed)
Old mothane to mild vs moderate to very severe (predicted)

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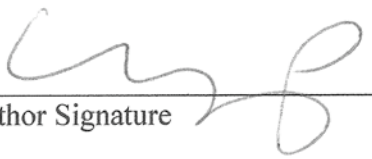

Author Signature

6/1/11

Date