Published in final edited form as:
J Clin Epidemiol. 2009 July ; 62(7): 716–724. doi:10.1016/j.jclinepi.2008.09.007.

Response Analysis for Multiple Symptoms Revealed Differences between Arms of a Symptom Management Trial

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Abstract

Objective—To describe the methodology of evaluating the response of cancer patients to interventions directed at lowering severity of multiple symptoms and compare two arms of a symptom management trial to determine factors associated with response and time to response.

Study Design And Setting—Randomized trial comparing a nurse assisted symptom management (NASM) cognitive behavioral intervention with an automated telephone symptom management (ATSM). Patients in both arms received 6 intervention contacts over 8 weeks. Analyses of the intervention contact data for 190 patients in NASM arm, and 164 patients in the ATSM arm were conducted. Severities of 15 cancer-related symptoms were assessed at each intervention contact and an anchor-based definition of response was adopted. Analyses were carried out using generalized estimating equations and Cox marginal proportional hazard models.

Results—When compared with patients in the NASM, patients in the ATSM had better response to managing anxiety, depression, poor appetite, cough and fatigue. NASM was more successful managing cancer pain. Response and time to response were associated with several patient and disease characteristics.

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Conclusion—The approach described here presents an analytic and clinical improvement over methods that examine each symptom separately or use summed scores of severity.

Keywords

Cancer; Symptom Management; Intervention; Symptom Response; Time to Response

What is new?

- The evaluation of interventions directed at the management of multiple cancer-related symptoms faces several methodological challenges related to summing severities across multiple symptoms or using absolute or percent change in severity.
- A new methodology of evaluating response to symptom management interventions is proposed using anchor-based definition of symptom response.
- The application of this methodology to the analysis of a trial of a cognitive behavioral intervention revealed differences between trial arms with respect to symptom response and time to response.
- The methodology that incorporates multiple symptom response outcomes can be applied to the analysis of symptom management trials in cancer.

Introduction

Among cancer patients, effective management of multiple symptoms is a key to maintaining therapeutic effective dosing, and improving patients' quality of life. [1-6] Research has examined single symptoms, [4-15] or groups of symptoms. [1-2,16-23]. Single symptom assessments may underestimate patients' total symptom severity burden. Since symptoms may be interrelated as a function of disease, treatment or patient characteristics, [24] the associations among symptoms must be taken into account when responses to interventions are evaluated at the patient level. Some patients may respond differently to interventions directed at different combinations of symptoms thus requiring more or less time to resolve different sets of symptoms.

When multiple symptoms are evaluated, their severities may be summed to produce an index across an array of symptoms. [25-30] The summed symptom severity scores measure the symptom severity burden but have several shortcomings such as equal contribution of symptom ratings toward total burden scores.

Clinically important cut-points separating moderate from mild, and severe from moderate pain, [31-34] and fatigue, [4,6] have been established demonstrating that increase or decrease of one unit on the rating scale may have different meaning depending on where on the scale the increase occurs. In prior work, [35] the authors established mild, moderate, and severe categories for 15 symptoms experienced by cancer patients undergoing chemotherapy based on their reports of symptom interference with enjoyment of life, relationships with others, general daily activities, and emotions. The cut-points were different for different symptoms, and provided consistent differentiation of the levels of interference over time. [36]

In this work, we define responses to the symptom management interventions based on shifts among the pre-defined mild, moderate and severe categories. These responses are symptom specific and anchor-based. Other definitions of response [37-39] are based on absolute or percent decline in severity. Patients who report a decline in pain from 33% to 50% are

considered to have achieved a clinically significant improvement. [40-41] Patients who reported that they were “much improved” or “very much improved” experienced approximately 30% reduction in pain. [37-38] However, such responses include reductions from a severity of 9 to a severity of 6 (33%) on a 0−10 severity scale which is not a satisfactory clinical outcome because pain remains at a distressing level. [42]

Two outcomes are evaluated in this work: a binary response versus non-response, and a continuous time to response for each symptom within a patient. Analyses are conducted by aggregating symptoms to the patient level and accounting for associations among them. Time to event type of outcomes such as survival time, time of disease-free survival, time to recurrence or time to treatment failure have been used in studies testing effects of various therapies and chemotherapeutic agents. [43-44] However psycho-educational or cognitive-behavioral interventions have not included time to response or time to other events as outcomes.

Two interventions are considered in this work: 1) A Nurse Assisted Symptom Management (NASM) intervention, and 2) an Automated Telephone Symptom Management (ATSM) intervention. Their effects on reduction in summed symptom severity are described in detail elsewhere. [45] Briefly, there were no differences between the arms in summed index of symptom severity or in severity of any symptom at the post-intervention interview. Both arms produced clinically significant improvement from baseline to 10 weeks. In this secondary analysis, we look beyond baseline and endpoint observations toward comparing arms according to symptom response and time to response to prescribed interventions.

Our analyses are guided by the following research questions: 1) Compared to ATSM, does the NASM produce better responses to symptom management strategies and shorter time to response at the level of the patient? 2) Do symptom factors such onset time, and patient factors such as comorbidity and the number of moderate and severe symptoms influence response and time to response?

Methods

Sample and Setting

The study was approved by the Institutional Review Board (IRB) of the sponsoring university and IRB's of the participating sites. Inclusion criteria were 1) being 21 years of age or older, 2) having a diagnosis of a solid tumor cancer or non-Hodgkins lymphoma, 3) be undergoing first course of chemotherapy, 4) being able to speak and read English, and 5) having a touchtone telephone. Patients agreeing to participate signed an informed consent form and were screened for symptom severity using an automated voice response version of M.D. Anderson Symptom Inventory. [25] Those who scored 2 or higher on any symptom in screening entered the trial, had an intake interview, received a copy of the Symptom Management Guide (SMG), and were randomized into either the NASM or the ATSM using computer minimization program [46] that balanced the arms with respect to recruitment location and site of cancer. Both arms of the trial received 6 calls over 8 weeks. At 10 weeks, outcome data were obtained through a second interview. In this analysis data collected during intervention contacts were used. We included patients who reported at least one symptom at moderate or severe level with at least one follow-up contact to evaluate the response of the interventions delivered for the symptom(s). Figure 1 summarizes the number of enrolled and attrited patients at each step, the number of cases meeting entry criteria and number analyzed.

Intervention

The trial sought to compare the impact ATSM intervention with a NASM protocol on reducing patient reports of severity of 15 prevalent symptoms [16-17,25-30,47]: fatigue, pain, dyspnea,

insomnia, anxiety, depression, nausea/vomiting, difficulty remembering, lack of appetite, dry mouth, peripheral neuropathy, diarrhea, cough, constipation, and weakness.

Following symptom management guidelines, [42] patients who rated severities of symptoms at 4 or higher at each contact received strategies to manage those symptoms. For patients assigned to the NASM group, nurses delivered up to four strategies for each symptom supplemented with references to the SMG. At each subsequent contact, assigned strategies were evaluated. Successful strategies were continued, and those not tried or tried but not deemed successful were dropped or replaced by different strategies.

In the ATSM arm, patients were called and queried by the automated system to rate severity of each symptom by pressing the appropriate numbers on their telephone keypads. For symptoms rated at 4 or higher, patients were directed to the section of the SMG that informed them about strategies to manage each symptom. For all symptoms with severities above 4 on the prior contact (except first), patients reported if the strategies from SMG were tried, and if tried, if they were helpful.

Measures

Age, sex, site and stage of cancer were obtained from the patients' medical records, and confirmed in baseline interview.

Comorbid conditions were assessed at baseline using a 15 item questionnaire modified from the one developed by Katz. [48] Number of comorbid conditions was dichotomized at the median into 0−2 versus 3 or more categories.

Severities of 15 symptoms were scored by patients on a scale ranging from absence (0) to the worst severity possible (10) at each of the 6 intervention contacts. Interference-based cut-points established by this team [35-36] were applied to categorize severity of each symptom as mild, moderate, or severe. Patients who reached moderate or severe levels on a symptom were classified as responders to the interventions strategies if they moved from; severe to moderate or to mild (or none), or moderate to mild (or none) between onset time (date of the first contact when symptom was at moderate or severe) and the last contact completed. Patients who went from moderate at onset to moderate or severe at the last contact, or from severe at onset to severe on the last contact, were classified as non-responders. Patients who never had a symptom at a level above mild, did not receive any interventions for the management of that symptom, were not classified as to response, and were not included in the analysis. Similarly, patients who had symptom onset at their last contact were not included in the analysis since no follow-up contacts were available to evaluate their response. Non-responders' time to response was treated as censored; for responders, time in days from the symptom onset (described above) to the date of the contact when patients reported first sustained improvement (e.g. going from moderate to mild, and staying mild for the remaining contacts) was defined as time to response.

The total symptom burden was assessed by determining the number of symptoms that ever reached moderate or severe during the intervention contacts. This number was dichotomized at the 3rd quartile as less than 8 versus 8 or more symptoms.

Data Analysis

The baseline equivalence and equivalence of attrition by the arms of the trial were established earlier. [45] To explain response versus non-response across multiple symptoms, a Generalized Estimating Equations (GEE) model with compound symmetry correlation structure [49] was used. Patient symptom was the unit of analysis. For the covariates in the model; trial arm, comorbidity, total symptom burden, and onset time of each symptom, dummy variables were

created to allow beta coefficients to vary across multiple symptoms to model possibly different effects of covariates across symptoms. The equality of beta coefficients across symptoms was tested for each of the covariates in the model using generalized score tests. [50-51] Because of reported unticonservatism of score tests, [53] we evaluated the symptom-specific coefficients to note any effects that may not be significantly different from other symptoms statistically, but represent clinically meaningful findings. The final “hybrid” model was built that included covariates with coefficients that differed across symptoms, and covariates with coefficients set to be equal across multiple symptoms. The GEE model was fit using GENMOD procedure, SAS version 9.1. [54] Odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated for trial arm and covariates of interest.

Time to response analysis was carried out using marginal Cox proportional hazard models implemented in TPHREG procedure in SAS. The marginal approach of Wei, Lin, and Weissfeld [55] was used for the patient level analysis that aggregated multiple symptoms and was carried out using maximum partial likelihood estimates of regression parameters and a robust sandwich covariance matrix estimate to account for the intracluster dependence (symptoms clustered within patient). [56-57] Similar to the response versus non-response analyses, the effects of the covariates were tested for equality of betas across multiple symptoms using Wald's test, and the symptom-specific coefficients were examined. The final “hybrid” model included covariates with coefficients that differed across symptoms, and covariates with the coefficients set to be equal across an array of symptoms.

Results

Table 1 presents characteristics of the sample by trial arm. Among solid tumors, breast cancer was the most prevalent site of cancer; the majority of patients had advanced (late stage) disease and all were undergoing first course of chemotherapy at the time of enrollment. By the 10 week interview, 64% of patients in the NASM, and 61% of patients in the ATSM arm were still on chemotherapy. Those who finished or discontinued chemotherapy by the 10 week interview were on average 5 weeks away from the last infusion.

The interference-based categories of symptom severity for each of 15 symptoms are presented in Table 2. Patient symptom cases not included in this analysis did not differ by arm of the trial, including those who went from mild to none. More than half of the patients reported their symptoms at the first intervention contact at moderate or severe levels.

Based on the tests of the equality of betas across multiple symptoms in response versus non-response model (Table 3), the trial arm and symptom onset time were entered as symptom-specific, that is the final model included 15 dummy variables (one for each symptom) to model group effect, and 15 dummy variables to model onset time. The number of comorbid conditions, and number of symptoms that ever reached moderate or severe levels during the intervention were treated as patient-level variables with the same coefficients across symptoms.

Compared to the NASM, the ATSM arm was more successful in achieving response for anxiety, depression, poor appetite, cough and fatigue (Table 4). The NASM arm produced a greater response to managing pain. Varying magnitudes of ORs for arm of the trial support the decision to model trial arm using different coefficients for different symptoms.

In both arms of the trial, patients with fewer than 3 comorbid conditions were more likely to respond compared to patients with 3 or more; patients with 8 or more symptoms that reached moderate or severe levels during intervention period had lower probability of response compared to those with less than 8 symptoms. Onset time was associated with the probability of response for fatigue, peripheral neuropathy and difficulty remembering: presence of these

symptoms on the first intervention contact was associated with smaller probability of response compared to reaching moderate or severe levels for the first time on the second or later contacts.

In the analysis of the time to response, only the coefficients for trial arm were set to differ across symptoms based on the results of tests of equality of betas presented in Table 5.

The ATSM group produced a shorter time to response for poor appetite, depression, cough, fatigue and peripheral neuropathy (Table 6). Greater number of comorbid conditions, and greater number of symptoms that reached moderate or severe levels were associated with longer time to response. In addition, symptoms present on the first intervention contact took longer to resolve compared to "new' symptoms that first presented on second or later contact.

Discussion

The results presented in this paper underscore the importance of conducting the analyses of multiple symptoms experienced by cancer patient undergoing chemotherapy at a patient level where multiple symptoms are aggregated, correlations among them are accounted for, and the effects of patient, disease and treatment characteristics are summarized across an array of symptoms. When separate analyses for each symptom are conducted, there is a possibility, given the number of tests, that the findings could occur by chance alone. Also, while fatigue was reported at moderate or severe levels during the intervention by approximately 90% of patients, other symptoms such as diarrhea, vomiting, and cough have much lower prevalence, and sample size becomes an issue when investigating response and time to response for each symptom separately. When data are aggregated across symptoms to the level of the patient, symptoms are nested within patients, and patients with at least one symptom at moderate or severe level are included in the analysis ensuring larger sample size compared to separate symptom by symptom analyses, and the possibility of type I errors due to multiple testing no longer exists.

A possible explanation for the differences in response to the management of some symptoms is that the automated system delivered interventions that are direct, and are tailored to patient needs by referring patients to the specific sections of the symptom management guide. These interventions may be easier to follow for patients in contrast to the more numerous and potentially shifting interventions delivered by nurses. However, a symptom of pain is difficult to manage, [39] and the skills of nurses in tailoring interventions to specific patients resulted in better response compared to an automated system. When time to response was examined, no significant differences between trial arms were found for pain. One possible explanation is that even with nurses' skills, pain took fairly long to resolve.

Shorter time to response for poor appetite, cough, depression, and fatigue in the ATSM arm compared to NASM was to be expected since for these symptoms the rate of response was better in the ATSM, and therefore there were more censored observations in the NASM arm. When arms of a trial are equal in response to symptom management, time to response may provide an important distinction, and this was the case with peripheral neuropathy.

The associations found between patient and symptom characteristics and response and time to response suggests that future behavioral trials may adjust the intensity of dosing regimens for patients who enter trials with more comorbid conditions and experience more symptoms. The finding that fatigue, peripheral neuropathy and difficulty remembering that presented on the first contact had lower probability of response compared to onset on later contacts may be counter-intuitive since patients in both arms received interventions for these symptom from the very first contact, so greater probability of response may be expected. However, our results suggest otherwise.

Our definition of response is anchor-based: it uses the decrease in symptom severity between mild, moderate and severe categories. In this research transitions from severe to mild corresponded to at least 50% reduction in symptom severity. Moreover, transitions from moderate to mild correspond to at least 33% for cough, depression, dyspnea, fatigue, pain, difficulty remembering, and weakness. Thus, implicit in these responses are clinically significant reductions in symptom severity produced by both arms of this trial. [40]

Several limitations of this work should be noted. The trial did not include a control group. Time to response was measured using dates between intervention contacts and not the actual dates when the symptom first reached moderate or severe or improved.. Despite these limitations, the approach of evaluating symptom responses presented here represents both an analytic and a clinical improvement over methods that use distributional measures of improvement, or use severity measures that sum severities of multiple symptoms into an index. Using response categories, clinicians can evaluate symptom severity interventions appreciating both clinical and statistical referents of success.

ACKNOWLEDGMENT OF RESEARCH SUPPORT

This research supported by Grant CA79280 from the National Cancer Institute and in affiliation with the Walther Cancer Institute, Indianapolis Indiana.

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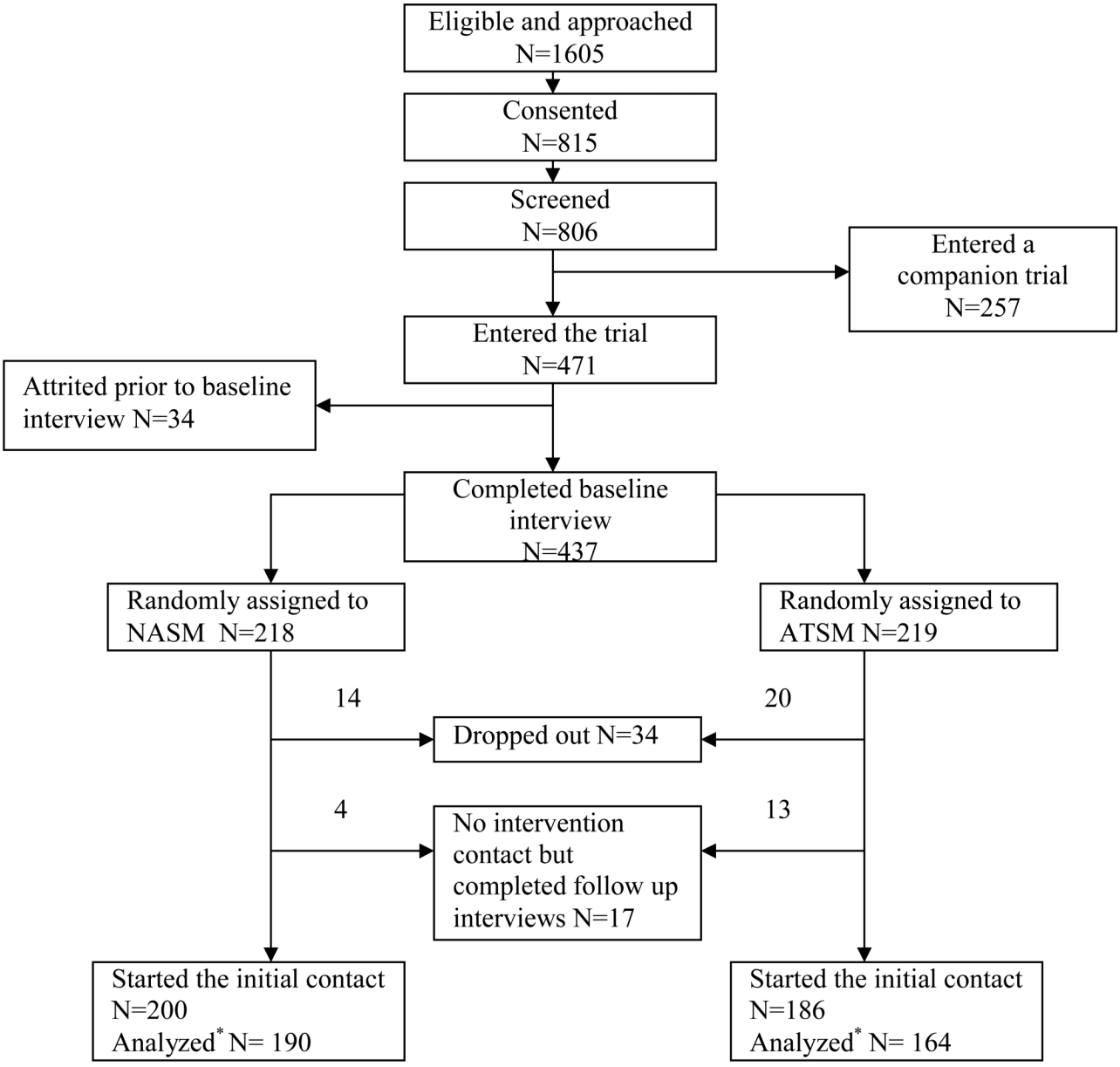

Analyzed*: Patients reported at least one symptom as moderate or severe and had a follow-up contact.

Figure 1.
Flowchart of the study.

Table 1

Characteristics of the sample by trial arm.

Variable	Category	NASM Arm		ATSM Arm	
		N	%	N	%
Patient Age	25 ~ 44	33	15.14	31	14.22
	45 ~ 54	57	26.15	62	28.44
	55 ~ 64	72	33.03	74	33.94
	65 ~ 74	38	17.43	27	12.39
	75 +	18	8.26	24	11.01
Education	High school or below	71	32.57	67	30.59
	Some college or technical training	72	33.03	66	30.14
	College	41	18.81	42	19.18
	Graduate professional degree	34	15.60	44	20.09
Cancer Site	Colon	30	13.76	33	15.07
	Breast	88	40.37	86	39.27
	Lung	39	17.89	37	16.89
	Other	61	27.98	63	28.77
Cancer Stage	Early	53	24.65	66	30.84
	Late	162	75.35	148	69.16
Metastatic Cancer	Yes	131	60.93	118	55.14
	No	84	39.07	96	44.86
Comorbidity	0~2	139	63.76	139	63.47
	3+	79	36.24	80	36.53
Number of Symptoms that Reached Moderate or Severe	Less than 8	126	66.32	104	63.41
	8 and above	64	33.68	60	36.59

Table 2

Mild, moderate and severe categories for symptom severity, symptom responses and onset times by trial arm.

Mild, moderate and severe categories of symptoms	Intervention Arm	Patient Response to Symptom Management		Not included in the analysis of response			Onset time[2]	
		Response	Non-Response	Remained mild	Not present	Onset on last contact[1]	1st contact	2nd or later contact
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Fatigue 0 1, 2−4, 5−10	NASM	82 (41.00)	95 (47.50)	3 (1.50)	6 (3.00)	14 (7.00)	144 (81.36)	33 (18.64)
	ATSM	95 (51.08)	63 (33.87)	10 (5.38)	8 (4.30)	10 (5.38)	148 (93.67)	10 (6.33)
Weakness 0 1−2, 3−4, 5−10	NASM	79 (39.50)	27 (13.50)	20 (10.00)	65 (32.50)	9 (4.50)	76 (71.70)	30 (28.30)
	ATSM	61 (33.52)	32 (17.58)	38 (20.88)	43 (23.63)	8 (4.40)	70 (75.27)	23 (24.73)
Depression 0 1, 2−3, 4−10	NASM	66 (33.00)	33 (16.50)	16 (8.00)	78 (39.00)	7 (3.50)	62 (62.63)	37 (37.37)
	ATSM	69 (37.50)	17 (9.24)	19 (10.33)	67 (36.41)	12 (6.52)	68 (79.07)	18 (20.93)
Difficulty Remembering 0 1, 2−4, 5 −10	NASM	63 (31.50)	41 (20.50)	18 (9.00)	71 (35.50)	7 (3.50)	77 (74.04)	27 (25.96)
	ATSM	46 (25.27)	30 (16.48)	24 (13.19)	73 (40.11)	9 (4.95)	60 (78.95)	16 (21.05)
Pain 0 1, 2−4, 5−10	NASM	68 (34.00)	29 (14.50)	10 (5.00)	76 (38.00)	17 (8.50)	61 (62.89)	36 (37.11)
	ATSM	45 (32.14)	36 (25.71)	21 (15.00)	30 (21.43)	8 (5.71)	58 (71.60)	23 (28.40)
Insomnia 0 1−3, 4−6, 7−10	NASM	64 (32.00)	22 (11.00)	52 (26.00)	53 (26.50)	9 (4.50)	63 (73.26)	23 (26.74)
	ATSM	56 (30.77)	19 (10.44)	62 (34.07)	38 (20.88)	7 (3.85)	61 (81.33)	14 (18.67)
Poor Appetite 0 1−3, 4−5, 6−10	NASM	69 (34.50)	19 (9.50)	27 (13.50)	74 (37.00)	11 (5.50)	51 (57.95)	37 (42.05)
	ATSM	71 (38.38)	11 (5.95)	53 (28.65)	38 (20.54)	12 (6.49)	61 (74.39)	21 (25.61)
Anxiety 0 1−3, 4−5, 6−10	NASM	55 (27.50)	19 (9.50)	61 (30.50)	58 (29.00)	7 (3.50)	45 (60.81)	29 (39.19)
	ATSM	56 (30.43)	9 (4.89)	66 (35.87)	46 (25.00)	7 (3.76)	48 (73.85)	17 (26.15)
Dyspnea 0 1−2, 3−6, 7−10	NASM	38 (19.00)	24 (12.00)	25 (12.50)	108 (54.00)	5 (2.50)	37 (59.68)	25 (40.32)
	ATSM	43 (23.12)	18 (9.68)	32 (17.20)	79 (43.41)	10 (5.49)	41 (67.21)	20 (32.79)
Dry Mouth 0 1−4, 5−8, 9−10	NASM	52 (26.00)	9 (4.50)	81 (40.50)	52 (26.00)	6 (3.00)	34 (55.74)	27 (44.26)
	ATSM	38 (20.88)	8 (4.40)	62 (34.07)	70 (38.46)	4 (2.20)	28 (60.87)	18 (39.13)
Constipation 0 1−3, 4−6, 7−10	NASM	36 (18.00)	10 (5.00)	35 (17.50)	113 (56.50)	6 (3.00)	29 (63.04)	17 (36.96)
	ATSM	52 (28.26)	9 (4.89)	55 (29.89)	60 (32.61)	8 (4.35)	46 (75.41)	15 (24.59)
Cough 0 1−2, 3−4, 5−10	NASM	37 (18.50)	20 (10.00)	35 (17.50)	103 (51.50)	5 (2.50)	37 (64.91)	20 (35.09)
	ATSM	45 (24.46)	4 (2.17)	46 (25.00)	82 (44.57)	7 (3.80)	30 (61.22)	19 (38.78)
Peripheral Neuropathy 0 1−3, 4−7, 8 −10	NASM	23 (11.50)	24 (12.00)	43 (21.50)	103 (51.50)	7 (3.50)	28 (59.57)	19 (40.43)
	ATSM	40 (21.98)	14 (7.69)	55 (30.22)	66 (36.26)	7 (3.85)	28 (51.85)	26 (48.15)
Nausea/Vomiting 0 1−3, 4−6, 7−10	NASM	36 (18.00)	5 (2.50)	39 (19.50)	114 (57.00)	6 (3.00)	19 (46.34)	22 (53.66)

Mild, moderate and severe categories of symptoms	Intervention Arm	Patient Response to Symptom Management		Not included in the analysis of response			Onset time[2]	
		Response	Non-Response	Remained mild	Not present	Onset on last contact[1]	1st contact	2nd or later contact
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	ATSM	38 (20.88)	12 (8.79)	51 (28.02)	76 (41.76)	5 (2.75)	33 (66.00)	17 (34.00)
Diarrhea 0 1−3, 4−5, 6−10	NASM	27 (13.50)	5 (2.50)	31 (15.50)	132 (66.00)	5 (2.50)	12 (37.50)	20 (62.50)
	ATSM	23 (12.57)	6 (3.28)	64 (34.97)	87 (47.54)	3 (1.64)	17 (58.62)	12 (41.38)

Onset on last contact[1]: Symptom reached moderate or severe for the first time at the last contact, no follow-up contact.

Onset Time[2]: Intervention contact when symptom reached moderate or severe level for the first time.

Table 3

The test of equality of coefficients across symptoms in GEE model of response versus non-response.

Covariates	Levels	Degrees of freedom	Wald Chi-Square	p-value
Trial arm	ATSM vs. NASM	14	31.03	<0.01
Number of comorbid conditions	3 and above vs. less than 3	14	21.26	0.10
Number of symptoms that reached moderate or severe	8 and above vs. less than 8	14	21.26	0.10
Onset time	1st contact vs. 2nd or later contact	14	38.24	<0.01

Table 4

Adjusted odds ratios of response derived from GEE model of response versus non-response for multiple symptoms.

Covariates	Symptom	Level	Ref. Level	Adjusted odds ratio (95% CI)	Chi-square p-value
Trial arm	Cough	ATSM	NASM	6.91 (1.89, 25.22)	<0.01
	Anxiety			2.65 (1.21,5.84)	0.02
	Poor Appetite			2.44 (1.19, 5.03)	0.02
	Depression			2.16 (1.11, 4.19)	0.02
	Dry Mouth			1.91 (0.78, 4.69)	0.16
	Constipation			1.85 (0.84, 4.06)	0.12
	Fatigue			1.75 (1.09, 2.80)	0.02
	Diarrhea			1.72 (0.57, 5.23)	0.34
	Peripheral Neuropathy			1.66 (0.80, 3.42)	0.17
	Dyspnea			1.24 (0.61, 2.51)	0.56
	Nausea/Vomiting			1.01 (0.44, 2.34)	0.98
	Difficulty Remembering			0.96 (0.53, 1.76)	0.91
	Insomnia			0.91 (0.44, 1.85)	0.79
	Weakness			0.64 (0.37, 1.10)	0.11
	Pain			0.48 (0.26, 0.88)	0.02
Number of comorbid conditions		3 and above	Less than 3	0.58 (0.44, 0.76)	<0.01
Number of symptoms that reached moderate or severe		8 and above	Less than 8	0.60 (0.46, 0.79)	<0.01
Onset time	Nausea/Vomiting	1st contact	2nd or later contact	1.67 (0.72, 3.86)	0.23
	Dry Mouth			1.51 (0.75, 3.05)	0.25
	Insomnia			1.50 (0.83, 2.70)	0.18
	Constipation			1.40 (0.75, 2.62)	0.29
	Weakness			1.27 (0.81, 2.00)	0.30
	Diarrhea			1.26 (0.47, 3.39)	0.64
	Poor Appetite			1.15 (0.67, 1.96)	0.62
	Anxiety			1.05 (0.58, 1.88)	0.88
	Pain			0.95 (0.56, 1.59)	0.84
	Cough			0.79 (0.39, 1.58)	0.50
	Dyspnea			0.78 (0.43, 1.41)	0.41
	Depression			0.73 (0.44, 1.22)	0.23

Covariates	Symptom	Level	Ref. Level	Adjusted odds ratio (95% CI)	Chi-square p-value
	Difficulty Remembering			0.59 (0.37, 0.93)	0.02
	Peripheral Neuropathy			0.44 (0.22, 0.86)	0.02
	Fatigue			0.28 (0.20, 0.40)	<0.01

Table 5

The test of equality of coefficients across symptoms in marginal Cox proportional hazard model of time to response.

Covariates	Levels	Degrees of freedom	Wald Chi-Square	p-value
Trial arm	ATSM vs. NASM	14	36.65	<0.01
Number of comorbid conditions	3 and above vs. less than 3	14	16.88	0.26
Number of symptoms that reached moderate or severe	8 and above vs. less than 8	14	10.53	0.72
Onset time	1^{st} contact vs. 2^{nd} or later contact	14	17.96	0.21

Table 6

Adjusted hazard ratios of response derived from Cox proportional hazard model of time to response for multiple symptoms.

Covariates	Symptom	Level	Ref. Level	Adjusted hazard ratio (95% CI)	Chi-square p-value
Trial arm	Cough	ATSM	NASM	2.11 (1.39, 3.20)	<0.01
	Peripheral Neuropathy			1.83 (1.13, 2.98)	0.01
	Depression			1.60 (1.17, 2.19)	<0.01
	Fatigue			1.49 (1.12, 1.99)	0.01
	Poor Appetite			1.38 (1.01, 1.88)	0.04
	Anxiety			1.34 (0.96, 1.88)	0.09
	Constipation			1.31 (0.88, 1.97)	0.19
	Dyspnea			1.23 (0.81, 1.85)	0.33
	Difficulty Remembering			1.09 (0.76, 1.58)	0.63
	Diarrhea			0.99 (0.59, 1.66)	0.97
	Dry Mouth			0.93 (0.63, 1.37)	0.72
	Weakness			0.93 (0.68, 1.27)	0.67
	Nausea/Vomiting			0.92 (0.60, 1.41)	0.70
	Insomnia			0.92 (0.66, 1.29)	0.64
	Pain			0.78 (0.54, 1.13)	0.19
Number of comorbid conditions		3 and above	Less than 3	0.77 (0.66, 0.91)	<0.01
Number of symptoms that reached moderate or severe		8 and above	Less than 8	0.69 (0.60, 0.80)	<0.01
Onset time		1st contact	2nd or later contact	0.75 (0.67, 0.85)	<0.01