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Irritable Bowel Syndrome: more than abdominal pain and bowel habit abnormalities

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Abstract

Background—Although irritable bowel syndrome (IBS) can be defined using few symptoms, principal symptoms alone may be inadequate in monitoring disorder severity. Secondary analysis of a published data set was performed to determine if more inclusive symptom measures would better reflect the burden of this disorder.

Methods—From a prospective naturalistic study of 213 patients meeting Rome II criteria, all the data was used from daily questionnaires recorded for 4 weeks, repeated again after an interval of 4 weeks. The total number of 11 symptoms and intensity grading score of each symptom was analyzed alongside individual symptom intensities by principal component analysis.

Results—The trend accounting for the most variance was explained by the intensity of all symptoms together. The second largest trend was explained by differences between IBS bowel habits (constipation and diarrhea). The 2 constipation and 4 diarrhea symptoms closely correlated within each group, but the ‘other’ symptoms were not correlated directly with either, and represent a separate dimension. ‘Other’ symptoms (pain/discomfort, abdominal uneasiness, flatulence/distension, incomplete evacuation, pain or burning in the stomach) were more highly correlated with disease intensity than either constipation or diarrhea symptoms. The sum of all symptoms and their intensity was consistent over each week, although the relative intensity of individual symptoms was more variable. Investigator measures of disease intensity underestimated that reported by patients.

Conclusion—Non-bowel habit symptoms include more than abdominal pain and discomfort, and contribute to the largest component of the total symptom burden. Thus, more than bowel habits and abdominal pain drive IBS symptom severity.

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Introduction

Irritable bowel syndrome (IBS) is a symptom-based disorder and thus is entirely dependent upon patient responses for diagnosis and assessment of therapeutic response. Three sets of diagnostic criteria have had wide distribution for IBS. The Manning criteria included abdominal pain and bowel habit symptoms, as well as other abdominal symptoms (incomplete rectal emptying, mucus per rectum, abdominal distension)¹. Rome I criteria focused more on pain and bowel habit-related symptoms but still allowed rectal mucus and distension to count toward the diagnosis². Rome II and Rome III criteria are more restrictive in that only abdominal pain and bowel habit-related symptoms count in making the diagnosis^{3,4}.

IBS is considered of heterogeneous origin, because the dominant symptoms at presentation and/or during the natural history of the illness differ between groups of patients and even within an individual patient. The importance of bowel habit heterogeneity has been highlighted by the partial response to medications that produce a major effect on bowel transit, either to decrease⁵ or increase it⁶. Attempts to bring clarification to the classification of IBS by use of bowel pattern predominance (diarrhea-predominant or constipation-predominant) have gained some degree of acceptance, but these sub-groupings have not yet been clinically validated⁴. The distribution of IBS subtypes based on bowel habits appears to be dependent upon the population studied, the geographical location, and the criteria used to define the bowel habit-based subtypes⁷. Most of the symptoms in these studies were mild to moderate, and appeared in clusters lasting 4–5 days per week on average for pain or bloating and 1–2 days per week for altered stool form. Many studies have relied on ROME I or II diagnostic criteria. In one study where 11 symptoms were recorded daily, nearly 90% of the patients had high frequency of multiple symptoms, as defined by having at least one symptom for more than 50% of the time⁸.

IBS symptoms are not stable with time and they vary in intensity. Patients with either diarrhea or constipation reported more frequent alternation between diarrhea and constipation as the more dominant symptom⁸. A symptom questionnaire repeated two years apart found that only 30% of patients had the same bowel symptom pattern in both surveys⁹. In another report, only 12 of 135 patients with IBS by Rome I criteria could be classified as either diarrhea- or constipation-predominant¹⁰.

Many IBS patients have a bowel-habit pattern that alternates between constipation and diarrhea, or is perceived in that way. “Alternators” can have rapidly fluctuating symptoms, often associated with psychological co-morbidity¹¹. Nearly half of the 1,102 patients in this large retrospective study had multiple extra-abdominal symptoms, including urinary symptoms, fatigue, and muscle symptoms; 60% were classified as somatizers on the SCL-90 scale. IBS patients often report symptom clusters that are not bowel-based, particularly those associated with general illness and indigestion¹². There is overlap between IBS and other symptom-based syndromes that also report symptoms of general illness and somatic symptoms referred to other organs. These disorders include both somatic (e.g. fibromyalgia and tension headache) and psychiatric (e.g. anxiety and depression) syndromes.^{13,14}

These studies suggest that symptoms beyond abdominal pain and bowel habit abnormalities are associated with IBS. The current best documented endpoint for IBS studies, ‘adequate relief’, may reflect the relative contribution of multiple symptoms, and the dominant symptom is likely to vary between patients¹⁵. However, it is not possible to ascertain from existing studies the relative importance of various symptoms toward total symptom burden. The validated methods for estimating severity in IBS patients utilize only a limited palette of abdominal symptoms¹⁶. To determine the value of abdominal symptoms beyond pain and

bowel habit abnormalities, we performed an analysis of the database from a previously reported study, as 11 symptoms were recorded; 6 symptoms dealt with bowel habit abnormalities and one with pain⁸. Principal component analysis is a method for reducing the dimensionality of a dataset that enables identification of underlying trends, and does so without losing any information. The analysis showed that all the data from 11 symptoms (occurrence and intensity of symptoms) were important in defining the disease burden of IBS, not just those symptoms associated with bowel habits (diarrhea or constipation) or pain alone.

Methods

Patients and symptom recording

213 IBS patients were enrolled across 30 centers. For two periods of 4 weeks duration patients recorded the severity of their symptoms (none/mild/moderate/severe) as a categorical response on a daily basis. There were 10 symptoms recorded and the number of bowel movements comprised an 11th measurement. These symptoms were selected to include all the symptoms included in the Rome II assessment of IBS³ plus two symptoms to interrogate the possibility of coexisting upper gut disorders (epigastric pain, heartburn). The severity responses were translated to numbers as none = 0, mild = 1, moderate = 2 and severe = 3. In the analysis the symptoms are referred to using four letter abbreviations: pain = non-epigastric abdominal pain or discomfort, soli = soft or liquid stools, lava = go to the lavatory more than normal, cons = very hard stools or can't go, push = did you have to push a lot?, urge = urgency, abdo = abdominal uneasiness, flat = flatulence, bloating, or distension, inco = incomplete evacuation, burn = epigastric pain or burning, move = number of daily bowel movements. The number of symptoms recorded in a day (Symp), max=10, and the summation of the severity scores across symptoms in a day (SymS) were calculated for each subject. These global assessments were also included in the analysis. Baseline assessments were made by a doctor for each symptom for each subject in the studies. For purposes of analysis, the 10 symptoms were categorized to identify bowel habit abnormalities as they have been used by the Rome committees to identify constipation- and diarrhea-predominant IBS, as follows: 2 of the symptoms were those identifying constipation (Push, Cons), 3 symptoms identifying diarrhea (Soli, Urge, Lava), and 5 identifying other abdominal symptoms that were not classifiable as either constipation or diarrhea (Inco, Pain, Abdo, Flat, and Burn).

Because IBS is an entirely symptom-based disorder, subjects with no symptoms arguably do not have IBS. Including these subjects could bias the interpretation of results when the analysis is trying to make inferences on the population of IBS subjects. In the first study period of 4 weeks, nine subjects out of the total of 213 had no symptoms and were excluded from the analyses, reducing subject numbers to 204. In the second study period of 4 weeks, thirty subjects out of the total of 213 had no symptoms and were similarly excluded from the analyses, reducing subject numbers to 183. Seven of the 8 subjects excluded from study period one were also excluded from period two.

Principal Component Analysis (PCA)

Five Principal Component Analyses were performed on the data generated from each study period. PCA is a statistical method for reducing the dimensionality of a dataset enabling the user to identify and interpret major underlying trends (components)¹⁷. It allows the user to visualize multidimensional data without losing information, to identify variability and trends, to identify correlations among the variables and to identify similarities/differences among the individuals' symptom profiles. All variables were centered and scaled to unit

variance prior to analysis to give equal weight to variables within the analysis. Symptom data was analyzed at the daily, weekly and monthly (4 week) levels.

For the daily analysis, the 28 daily measures (one for each day of the 4 week period) for each of the 10 symptoms (280 variables), plus Move, Symp and SymS (28 variables each) were used (364 variables in total). For the weekly analysis, the daily severity scores for each of the responses used in the first analysis were summed over each of the 4 weekly periods. These weekly scores for each of the 13 responses were used as variables (52 variables in total). For the monthly analysis, the weekly severity scores for each of the responses used in the second analysis were summed, producing just one response per symptom for each subject (13 variables). The ten monthly symptom responses were combined with the baseline/doctors assessments of the same symptoms. The 20 responses were used as variables in a fourth PCA. The 13 monthly responses were combined with the three global assessment measures. These 16 responses were used as variables in a fifth PCA.

All models were assessed for their goodness of fit by reviewing the variation explained by the principal components (R^2), the variation that can be predicted by the model (Q^2) and the distance to the model (DModX) (residuals in multi-dimensional space). The principal components (PC) are always extracted in decreasing order of importance; the first PC contains the more information than the second PC, etc. There is also no correlation between the information contained in the different PCs.

Interpretation of the principal components identified by the models was performed by plotting scores and loadings. Each variable is given a weight in each new component. This value is called a loading and tells how important that variable is in the new component. Variables with greater degrees of variability are given larger loadings. Variables with similar loadings are more positively correlated than those further apart and those diagonally opposite each other in a loadings plot are negatively correlated. Variables that contribute little to the PC have small loading values and are found near the center of the loading plot.

Score plots are reflections of information related to subjects, whereas loading plots provide information about the variables within the data set. Each subject is given a value for each new principal component. This value is called a score and is calculated as a combination of the original variables using the loadings as weights. Individuals with similar scores have similar profiles across symptoms and will be close to each other on a scores plot. The reason subjects group together or are far apart from each other is interpreted by relating their positions in the scores plot to the positions of the variables in the loadings plot. Additionally, profiles of each symptom can be plotted on a contributions plot. Each bar in such a plot represents how far the subject deviates from the average for a particular variable. All analyses were performed using SIMCA-P software (Version 11.0.0.0, copyright © Umetrics AB.)

Results

Principal component identification

Three major trends (components) were identified from the PCA for the daily, weekly and monthly analyses. 1) total disease symptoms/intensity of all 10 of the symptoms elicited and movements, 2) difference between IBS bowel related symptoms (constipation and diarrhea), and 3) 'other' abdominal symptoms. Three additional minor trends were identified in the daily and weekly analyses. These were related to time but only explained a few percent of the total variation. In the monthly models these trends can not be seen as data is compacted over time.

The variation explained showed remarkable consistency in the two study periods (Table 1). Because of this finding, only the analysis of data from period 1 will be included in this paper. As summary periods increased from daily to weekly to monthly the proportion of the variability explained by each component increased (Table 1). This is because the summarization increasingly reduces the random variability.

Components 1 and 2

All variables have positive loadings in the first component indicating that they all contributed positively to the variation of this first component (Figure 1). A subject with a high score in this first component (e.g. subject 916 in Figure 2) will have high responses in most variables on this loadings plot. The two variables that account for the highest proportion of the variation within this component were the number of symptoms on a given day (Symp) and the total severity of symptoms (SymS). Although this seems self-evident, it means that no sub-grouping of symptoms dominated this first component. The ‘other’ abdominal symptoms (pain/discomfort, abdominal uneasiness, flatulence/distension, pain or burning in the stomach) were more correlated (had a higher positive value) with the disease intensity component (Component 1) than either the constipation or diarrhea symptom groups (Component 2).

The loadings in the second component split into three distinct groups; 1) the constipation symptoms [(Push, Cons) which had large negative loadings], 2) the diarrhea symptoms [(SoLi, Urge, Lava) and the number of movements (Move) which had large positive loadings], and 3) the symptoms shared by subjects with either Constipation and/or Diarrhea [(Inco, Pain, Abdo, Flat, Burn), the number of symptoms (Symp) and the overall severity of symptoms (SymS) which have small either negative or positive loadings] (Figure 2). A subject with a high score in this second component (e.g. Subject 251 in Figure 2) will have high responses in the diarrhea symptoms and low response in the constipation symptoms. A subject with a low score in the second component will have the reverse profile of symptoms.

Figure 2 shows the scores derived from the loadings in Figure 1 for each subject identified by number over the first 28 day period. In Figure 2 the subjects became more variable in the second component (severity of constipation/diarrhea bowel habit abnormalities) as their scores in the first component (severity of IBS symptoms) increased. The more severe the global symptoms are, the more likely an individual patient is to be of a type. The striking aspect of Figure 2 is that over 95% of the subjects are accounted for by a single cluster distributed around the neutral point in the plot. The clusters labeled ‘severe diarrhea’ and ‘severe constipation’ comprise only a handful of subjects with symptoms that are severe enough to drive the scores to the extreme edges of the scores plot (see Figure 1). The same patterns for the first and second components are consistently reproduced in the loadings and scores plots for the weekly and monthly analyses for both periods (data not shown).

Component 3

Component 3 is the variance accounted for by the ‘other’ abdominal symptoms (Pain, Abdo, Flat, Burn). The loadings in the third component when plotted against the second component (Figure 3) show that the ‘other’ abdominal symptoms did not contribute to the variation produced by the two IBS bowel habit types (close to zero in component 2) and represented a separate dimension (Component 3). Incomplete evacuation (Inco) did track in the lower quadrants of the graph, consistent with association with altered bowel habits, but this symptom clustered in between constipation (left side) and diarrhea (right side), albeit somewhat closer to the cluster of constipation symptoms. Thus, this symptom of incomplete evacuation to a limited extent may be a component of either the constipation or diarrhea complex of symptoms, but on the whole slightly more correlated with constipation

symptoms than diarrhea. The scores plot (Figure 4) of components 2 and 3, showed clustering of nearly all the subjects into one homogeneous group spread around the center of the plot. Very few subjects are found on the periphery of the plot, corresponding to the following groups: a) constipation with no other symptoms, b) constipation with other symptoms c) diarrhea with no other symptoms and d) diarrhea with other symptoms. The largest group of subjects was found in the centre of this plot, implying that they either have very few/mild symptoms or have a mixture of IBS symptoms.

Changing patterns with time

The number of symptoms (Symp) and the overall severity of symptoms (SymS) were good overall measures for IBS regardless of the type of bowel habit (Figure 1). On a daily basis the number of symptoms was well distributed among the population of patients, and each additional symptom from 1–7 per day represented about 12% of the total patient population (Figure 5, curve on the far left). However, as these measures were summarized over larger time periods the number of symptoms became increasingly insensitive as more of the population experienced most if not all of the symptoms (Figure 5, middle and right hand curve). Rather few patients had 8–10 symptoms on a daily basis, but most patients had multiple symptoms at some time during the month. Approximately 5% of subjects experienced 9 or more symptoms on a day, whilst 35% of subjects experienced 9 or more symptoms in a week and almost 70% of subjects experienced 9 or more symptoms in a month. The total severity scores were not restricted in this way. Time trends in this study came through in the 4th, 5th and 6th components of the daily and weekly analyses. These were very small relative to other trends explaining just a few percent of the total variation (see Table 1) and are therefore much less important.

Subject Profiles

Profiles of individual subjects illustrate the different types of profiles discriminated by the second component on a contributions plot (Figure 6). These weekly profiles also demonstrate the consistency observed from week to week.

Baseline/doctors assessment

At recruitment to the study a baseline assessment was made by the doctor for each symptom. Figure 7 is a loadings plot of the first two components, summarizing for each variable the physician and subject assessments over a month. The plot shows a clear reduction in loadings for severity of each symptom assessed by the doctor in the first component, i.e. as a component of total disease severity. Not only were the ‘other’ non-bowel habit related symptoms (e.g. pain, burning) perceived as less severe by the physician, but this difference was found even for the symptoms associated with diarrhea and constipation. In the second component (which accounts for less of the variation) the loadings for diarrhea and constipation by themselves were very similar for both the patient and the doctor. Thus, the doctors’ assessment was an underestimate of the patient’s response on severity, but they could clearly identify patients with severe aberrations in bowel habits.

Discussion

Making a diagnosis of irritable bowel syndrome is based primarily on self reported symptoms, and has become fairly routine for gastroenterologists and many other physicians². The requirements for diagnosis according to the Rome II criteria include abdominal pain or discomfort and a change in bowel habits, linked with the pain or discomfort³. The diagnosis is fairly stable with time¹⁸. However, it has been difficult to demonstrate a large effect of treatment on pain, either by itself or as a global assessment of irritable bowel-associated pain or discomfort¹⁹. Pain in particular has not been a consistent

symptom in IBS, nor in patients with chronic abdominal wall pain uncomplicated by any change in bowel habits²⁰. Nearly half of the 137 patients reported by Costanza et al had no abdominal pain at 1 year of follow up. However, pain was not an isolated symptom, as non-gastrointestinal co-morbidity was high.

The findings from the present study provide an initial interpretation to these discrepant findings. First, the severity of symptom burden was related more to all symptoms recorded, not just to pain or to specific changes in bowel habits. PCA is designed to simplify by reducing the dimensionality. If the loadings of a symptom in these new components are small, then they contribute little to the newly identified trends. It is often the case that the first component explains a common correlation across all variables in the analysis, but this is not always the case. In this study it might have been thought *a priori* that symptoms related to IBS subtypes (e.g. C- or D-IBS) would have been the dominant component, but this was not found.

Second, the overall pattern of symptoms was consistent over a month, but individual symptoms fluctuated during that time. These findings suggest that when patients record their overall irritable bowel-related pain or other symptoms (as in the ‘adequate relief’ endpoint, they could be integrating their response to all symptoms into the answer. The daily data based on a 4 point scale are the most variable and hence the least clear when assessing underlying trends, and in addition are less sensitive to differences between patients. Weekly and monthly totals were measured on a 22- and 85-point scale, respectively. It also seems that patients rate the severity of all symptoms (including those related to bowel habits) as greater than do their physicians. Thus, for most patients, the symptoms of diarrhea and constipation may have an affective component, as do the symptoms of pain or burning. What a patient feels and what can be objectively demonstrated for bowel habits may be influenced by the same cortical filtering as occurs for pain responses.

The ‘other’ abdominal symptoms (pain or discomfort, abdominal uneasiness, flatulence or distension, incomplete evacuation, and epigastric pain or burning in the stomach) clustered with each other, but not with the altered bowel habit. Some of these symptoms, especially flatulence and incomplete evacuation, have been attributed to alterations in motility and by inference with altered bowel habits. However, analysis by PCA does not support that any of these symptoms explains the variance associated with either pattern of altered bowel habits (i.e. constipation or diarrhea). By inference these data do not support that any of these ‘other’ abdominal symptoms is the result of an altered motility leading to slower or more rapid intestinal transit.

There were 5 symptoms dealing with bowel-habit abnormalities (including both constipation and diarrhea) and 5 related to other abdominal symptoms. Thus, the result of the groupings seen in Figures 1 and 2 do not result from asking about more symptoms in the ‘other’ category. It is accepted that these variables are not independent, however. They are correlated to lesser or greater degrees, and it is precisely these interdependencies that are investigated in the PCA analysis. The PCA pulled out 3 underlying trends to which all symptoms contribute to a greater or lesser degree, depending upon their correlation.

The current study demonstrates the potential value of including all abdominal symptoms in an assessment of disease severity or disease burden. This more inclusive view of IBS symptoms may take on more importance as the degree of co-morbidity becomes increasingly documented in patients with IBS²¹. Not only are non-gastrointestinal somatic symptoms found in patients with IBS, but so are psychiatric symptoms^{22,23}. Some studies suggest that non-abdominal symptoms (e.g. feeling tense, tiring easily, difficulty sleeping) may be better predictors of severity than bowel-habit symptoms²⁴. These symptoms were

not recorded in the present data set, but need to be in future studies. Such studies will be needed to determine if a more inclusive approach to symptoms is useful in determining course and response to treatment, and/or if it is useful or important to include not just other abdominal symptoms, but somatic symptoms from other organs, and even psychiatric symptoms.

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Abbreviations

IBS	irritable bowel syndrome
PCA	principal component analysis

References

1. Manning AP, Thompson WG, Heaton KW, et al. Towards a positive diagnosis of the irritable bowel. *Br Med J*. 1978; 2:653–4. [PubMed: 698649]
2. Drossman, DA.; Richter, JE.; Talley, NJ.; Thompson, WG.; Corazziari, E.; Whitehead, WE. The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment: A Multinational consensus. McLean, VA: Degnon Associates; 1994. (ROME I)
3. Drossman, DA.; Corazziari, E.; Talley, NJ.; Thompson, WG.; Whitehead, WE. Diagnosis, pathophysiology and treatment: A multinational consensus. 2. McLean, VA: Degnon Associates; 2000. ROME II. The functional gastrointestinal disorders.
4. Drossman, DA.; Corazziari, E.; Delvaux, M.; Spiller, RC.; Talley, NJ.; Thompson, WG.; Whitehead, WE. The Functional Gastrointestinal Disorders. 3. McLean, VA: Degnon Associates, Inc; 2006. Rome III.
5. Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomized, placebo-controlled trial. *Lancet*. 2000; 355:1035–40. [PubMed: 10744088]
6. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating, and constipation. *Aliment Pharmacol Ther*. 2001; 15:1655–66. [PubMed: 11564007]
7. Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome: systematic review. *Am J Gastroenterol*. 2005; 100:1–11.
8. Mearin F, Baro E, Roset M, Badia X, Zarate N, Perez I. Clinical patterns over time in irritable bowel syndrome: symptom instability and severity variability. *Am J Gastroenterol*. 2003; 99:113–121. [PubMed: 14687152]
9. Williams RE, Black CL, Kim H-Y, Andrews EV, Mangels AW, Budas JJ, Cook SF. Stability of irritable bowel syndrome using a Rome-II based classification. *Aliment Pharmacol Ther*. 2006; 23:197–205. [PubMed: 16393298]
10. Walter SA, Ragnarsson G, Bodemar G. New criteria for irritable bowel syndrome based on prospective symptom evaluation. *Am J Gastroenterol*. 2005; 100:2598–2599. [PubMed: 16279922]
11. Tillisch K, Labus JS, Naliboff BD, Bolus R, Shetzline M, Mayer EA, Chang L. Characterization of alternating bowel habit subtype in patients with irritable bowel syndrome. *Am J Gastroenterol*. 2005; 100:896–904. [PubMed: 15784038]
12. Bittner AC, Croffut RM, Stranahan MC. Prescript-Assist probiotic-prebiotic treatment for irritable bowel syndrome: a methodologically oriented, 2-week, randomized, placebo-controlled, double-blind clinical study. *Clin Ther*. 2005; 27:755–61. [PubMed: 16117982]
13. Robbins JM, Kirmayer LJ, Hemami S. Latent variable models of functional somatic distress. *J Nerv Mental Dis*. 1997; 185:606–15.

14. Nimnuan C, Rabe-Hesketh S, Wessely S, Hotopf M. How many functional somatic syndromes? *Psychosom Res.* 2001; 51:549–57.
15. Camilleri M, Mangel AW, Fehnel SE, Drossman DA, Mayer EA, Talley NJ. Primary endpoints for irritable bowel syndrome trials: a review of performance of endpoints. *Clin Gastroenterol Hepatol.* 2007; 5:534–540. [PubMed: 17428741]
16. Lembo A, Ameen VZ, Drossman DA. Irritable bowel syndrome: toward an understanding of severity. *Clin Gastroenterol Hepatol.* 2005; 3:717–725. [PubMed: 16233998]
17. Chatfield, C.; Collins, AJ. *Introduction to Multivariate Analysis.* Chapman and Hall; London: 1980. p. 57-79.
18. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. *Ann Intern Med.* 1995; 122:107–112. [PubMed: 7992984]
19. Jaiwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* 2000; 133:136–147. [PubMed: 10896640]
20. Costanza CD, Longstreth GF, Liu AL. Chronic abdominal wall pain: clinical features, health care costs, and long-term outcome. *Clin Gastroenterol Hepatol.* 2004;395–399. [PubMed: 15118977]
21. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology.* 2002; 122:1140–1156. [PubMed: 11910364]
22. North CS, Downs D, Clouse RE, Ahrakawi A, Dokucu ME, Cox J, Spitznagel EL, Alpers DH. The presentation of irritable bowel syndrome in the context of somatization disorder. *Clin Gastroenterol Hepatol.* 2004; 2:787–795. [PubMed: 15354279]
23. Walker EA, Gelfand AN, Gelfand MD, Katon WJ. Psychiatric diagnoses, sexual and physical victimization, and disability in patients with irritable bowel syndrome or inflammatory bowel disease. *Psychol Med.* 1995; 25:1259–1267. [PubMed: 8637955]
24. Spiegel BMR, Gralnek IM, Bolus R, Chang L, Dulai GS, Mayer EA, Naliboff B. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Arch Intern Med.* 2004; 164:1773–1780. [PubMed: 15364671]

Figure 1. Loadings plot of the first two components from the analysis of daily data in the first period

Each variable is represented 28 times, once for each day in the study. The abscissa represents the first component, $p[1]$, and the ordinate the second component, $p[2]$.

Figure 2. Scores plot of the first two components from the analysis of daily data in the first period

Each subject is labeled by a unique subject id number. The abscissa represents the first principal component, $p[1]$, and the ordinate represents the second principal component, $p[2]$. The central ellipse represents the Hotelling T^2 95% confidence interval.

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Figure 4. Scores plot of the second and third components from the analysis of daily data in the first period

The abscissa represents the second principal component, $p[2]$, and the ordinate represents the third component, $p[3]$. The central ellipse represents the Hotelling T^2 95% confidence interval.

Figure 5.
Cumulative percent of subjects with number of symptoms at daily, weekly and monthly periods for period 1.

Figure 6. Sample of subject profiles

Profiles of each symptom have been plotted on a contributions plot. Each bar shows the deviation of the subject from the average, in standard deviations, for the variables in the model.

Figure 7. Loadings plot of the first two components from the analysis of baseline and monthly measures in the first period

The sum of all the subject assessments for each variable is identified by the abbreviation for the variable next to the filled square (for subjects) and filled triangle (for physicians). The abscissa represents the first principal component, $p[1]$, and the ordinate represents the second component, $p[2]$.

Table 1
Proportion of variability explained by PCA models for different summary periods and two different study periods.

Component	Daily		Weekly		Monthly	
	period 1	period 2	period 1	period 2	period 1	period 2
1 severity	0.29	0.32	0.42	0.44	0.49	0.50
2 con/dia	0.09	0.10	0.14	0.16	0.18	0.19
3 other symp	0.04	0.04	0.06	0.06	0.07	0.07
4	0.03	0.02	0.04	0.03		
5	0.03	0.02	0.04	0.03		
6	0.02	0.02	0.03	0.03		