Study Protocol

Protocol for the evaluation and validation of Qi Blood Yin Yang deficiency pattern questionnaire: prospective observational study

Jihye Kim, Keun Ho Kim *

KM Fundamental Research Division, Korean Institute of Oriental Medicine, Daejeon, Korea

ABSTRACT

Background: The aim of this study is to validate the pattern identification standard of qi, blood, yin, and yang deficiency patterns diagnosis. The current study will investigate the usefulness of the Qi Blood Yin Yang deficiency pattern questionnaire as a diagnostic tool for qi, blood, yin, and yang deficiencies by assessing the agreement between the scores and a gold standard established by assessors.

Methods: This protocol is for a single center, prospective, observational study. A total of 248 eligible patients with unexplained chronic fatigue will be assigned to four groups in a 1:1:1:1 ratio as the qi deficiency group, blood deficiency group, yin deficiency group, and yang deficiency group. The primary outcome will be measured using the score of the Qi Blood Yin Yang deficiency pattern questionnaire and the secondary outcomes will be measured using the fatigue severity scale, Korean-translated chalder fatigue scale, computerized tongue image analysis system, and three types of pattern identification questionnaires (cold-heat, food accumulation, and seven emotions patterns). The safety of the clinical study will be assessed after measurements at every visit. All statistical analysis will be performed using the R Statistics program. Statistics experts will analyze the relationship between clinical data using the Pearson’s Chi-squared test and independent t-test.

Discussion: This study will provide reference data and good evidence that are applicable to future studies. Furthermore, the results of the present study are useful to improve the care of patients with unexplained chronic fatigue and unexplained chronic fatigue-related disorders.

© 2015 Korea Institute of Oriental Medicine. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Chronic fatigue (CF) generally refers to the status of subjective tiredness or to a lack of energy. CF is divided into explained CF and unexplained chronic fatigue (UCF) for which no medical explanation exists. UCF is classified as chronic fatigue syndrome (CFS) or idiopathic chronic fatigue (ICF). The diagnostic criteria for CFS are as follows: (1) duration of severe fatigue > 6 months; (2) other causes should be excluded; and (3) the individual concurrently has four or more of eight specific symptoms. These symptoms include the following: (1) headache; (2) migratory polyarthralgias; (3) myalgia; (4) postexertional malaise or fatigue (duration > 24 hours); (5) impaired short-term memory or concentration; (6) pharyngitis; (7) tender cervical or axillary adenopathy; and (8) nonrestorative sleep. Information about CFS can be found at http://www.cdc.gov/cfs/case-definition/index.html. Cases that cannot be categorized according to the above diagnostic criteria are included under ICF.

Several hypotheses have been proposed for the pathogenesis of UCF, including oxidative stress, hypothalamic–pituitary–adrenal axis abnormalities, and immune dysfunction. Despite the universality of UCF, the etiology, pathophysiology, nomenclature, and diagnostic criteria of UCF still remain unclear in the medical community. Several hypotheses have been proposed for the pathogenesis of UCF, including oxidative stress, hypothalamic–pituitary–adrenal axis abnormalities, and immune dysfunction. Despite the universality of UCF, the etiology, pathophysiology, nomenclature, and diagnostic criteria of UCF still remain unclear in the medical community.

The ultimate objective of diagnosis and treatments from the KM viewpoint is to help the individual recover balance in terms of the balance between the qi and blood conditions of the internal organ functions and of the coexisting yin and yang. The ultimate objective of diagnosis and treatments from the KM viewpoint is to help the individual recover balance in terms of the balance between the qi and blood conditions of the internal organ functions and of the coexisting yin and yang.

Similar to conventional medicine, in KM the clinical signs and symptoms are collected from the patients and interpreted to diagnose disease. However, KM practitioners diagnose diseases and prescribe treatments in terms of individual patterns of a syndrome, reflecting an individual’s overall body condition. Syndromes can be described as the pathological characteristics that an individual presents in response to pathogens, allergens, or other undesirable stimulation, whereas body constitution is used to describe one’s overall physical and psychological condition. An individual body constitution and the current health status can be considered in terms of the balance between the qi and blood conditions of the internal organ functions and of the coexisting yin and yang. The ultimate objective of diagnosis and treatments from the KM viewpoint is to help the individual recover balance in terms of the balance between the qi and blood conditions of the internal organ functions and of the coexisting yin and yang.

Similarly, UCF patients can be classified into deficiency syndrome or excess syndrome, which refers to the deficiency or excess in qi, blood, yin, and yang. Previous studies mentioned that UCF is mainly considered to exhibit the deficiency pattern and therefore most patients are treated by invigorating qi and yang and nourishing blood and yin. Treatments for people with UCF can be prescribed in consideration of their patterns of body constitution; most patients have been identified as having four pattern identifications (PIs) as follows: qi deficiency (QD), blood deficiency (BD), yin deficiency (YnD), and yang deficiency (YgD). Patients with UCF can receive specific medicinal treatments based on the deficiency patterns described above. Generally, the balance of qi, blood, yin, and yang is important for maintaining health and treating the diseases in KM clinics. However, no diagnostic tools, such as questionnaires or medical devices, have been validated in clinical trials.

Therefore, the aim of this study is to validate the Qi Blood Yin Yang deficiency pattern questionnaire (QBYY-Q) through a clinical study to determine the correlations between UCF and responses to the QBYY-Q.

2. Methods

2.1. Study design

This study will be conducted as a single center, prospective, observational study. This clinical study will consist of screening (Visit 1), Measurement 1 (Visit 2), Measurement 2 (Visit 3) and follow up (selected participants only). After participants complete the first measurement, eligible participants will be randomly selected for evaluating the test–retest reliability (repeatability) of the QBYY-Q. Thirty participants will be selected from the randomization list. A computer-generated, blocked random allocation sequence will be generated using a Microsoft Office Excel program (Excel 2013, Microsoft Office, USA) produced by the Korean Institute of Oriental Medicine, Daejeon, Republic of Korea. Random allocation will be performed after the first measurement of the participants who provide informed consent and meet the inclusion criteria. The selected participants will complete the QBYY-Q, pattern identification questionnaire (PI-Q), and fatigue questionnaire, and their tongue images will be captured using the Computerized tongue image analysis system within 3–5 weeks after Visit 2 (the first measurement). A flow diagram and study schedule for participants are depicted in Fig. 1 and Table 1.

CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; FSS, Fatigue Severity Scale; ICF, idiopathic chronic fatigue; KMD, Korean medical doctors; FSS-10item, Perceived Stress Scale-10item.

2.2. Recruitment of participants

2.2.1. Recruitment strategies

There will be three strategies in participant recruitment. Firstly, participants will be recruited by advertising on hospital websites and posters displayed in Won Kwang University, Gwangju Korean Medical Hospital. Secondly, printed recruitment posters will be distributed in public clinics and nearby communities. Thirdly, advertisements will be published in the local universities.

2.2.2. Participants

A total of 311 participants will be enrolled in this study. The participants that are residing in Gwangju will include 248 UCF patients and 63 control participants. They will go through telephone prescreening led by the clinical study coordinator, to ensure UCF patients meet the inclusion criteria: “men and women aged 20 years to 69 years” and “the presence of UCF that is continuous and repetitive for more than 6 months.” The next step is for participants to visit the clinical study center and to undergo a more indepth screening process to
Fig. 1 – Study schedule for participants. Participants with a diagnosis of unexplained chronic fatigue were recruited at the Won Kwang University of Traditional Korean Medicine. A total of 248 patients were enrolled to four groups: qi deficiency group A, blood deficiency group B, yin deficiency C, and yang deficiency D in a 1:1:1:1 ratio. The outcome was measured at every visit.

2.2.2.1. Inclusion criteria. Participants who meet the following criteria will be included: (1) men and women aged 20 years to 69 years; (2) the presence of UCF that has been continuous for > 6 months; (3) UCF (including CFS and ICF); (4) participants in agreement with the Korean medical doctors’ (KMDs) diagnoses; and (5) those who consent to participate in this trial and who sign an informed consent statement after listening to a clear explanation of the purpose and characteristics of this study.

2.2.2.2. Exclusion criteria. Participants with one or more of the following criteria will be excluded: (1) score ≥ 14 in the Perceived Stress Scale-10item; (2) patients in disagreement with KMDs’ diagnoses; (3) the presence of the following conditions in the participant’s past history that might trigger CF: (a) organic causes, such as acute or chronic liver disease (e.g., hepatitis, liver cirrhosis), anemia, tuberculosis, chronic lung disease, cardiovascular disease (e.g., heart failure, hypertension), endocrine/metabolic disease (e.g., diabetes, thyroid gland disease, severe obesity), autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis), malignant tumors, or infectious disease; (b) psycho-social causes, such as depression, anxiety neurosis, recent severe stress, schizophrenia, alcoholism, or an eating disorder (anorexia nervosa, bulimia nervosa); (4) participants who have taken the following drugs within the past 2 weeks: antihypertensive drugs, antidepressants, antianxiety agents, hypnotics, or antihistamines; (5) pregnant or breast-feeding women; (6) individuals participating in other clinical trials; (7) individuals who are overworked; (8) individuals who experienced a hypersensitive reaction after clinical laboratory test; (9) Declined to participate; (10) Other reasons.
test; (9) individuals who did not provide informed consent; and (10) others whose clinical trial conductors are considered inappropriate for participating in this study.7

2.2.2.3. Withdrawal criteria. Participants having one or more of the withdrawal criteria will be excluded as follows: (1) intolerance to worsening conditions; (2) quitting voluntarily; and (3) adverse medical events occurring during the study. If participants withdraw from the study either in the measurement or in the follow-up phase, the reason of withdrawal should be clarified and the rate should be statistically analyzed.

2.2.3. Sample size
Sample size calculation was based on the average effect sizes in one previous clinical trial of QBYY-Q for patients with UCF.13 With the level of statistical significance set at $p = 0.05$ and a study power of 90%, an estimated sample size was 56 participants per patient group and 56 participants per control group (total 280 participants). Considering a drop-out rate of 10%, the total sample size required is 311 (62 participants per patient group and 63 participants control group).

2.3. Diagnostic criteria

2.3.1. Diagnosis of UCF
Diagnosis of UCF occurs in mainly patients who have suffered from fatigue lasting > 6 months. The Centers for Disease Control and Prevention - 1994 criteria for CFS were used to distinguish between CFS and ICF, using the cutoff of four among the eight symptoms in the minor criteria, respectively. CFS patients should complain of major criteria symptoms and more than four of the minor criteria symptoms, and ICF patients should complain of major criteria symptoms but less than four of the minor criteria symptoms. If a patient complains of fatigue lasting > 6 months, headache, and pharyngitis, the patient is diagnosed as ICF.14

2.3.2. Diagnosis of PI
To date, there is no gold standard for the diagnosis of PI, although much of the KM literature has described common aspects of PI. Our previous study also demonstrated discrepancies in the diagnoses of QD, BD, YnD, and YgD among KMDs.13 To increase the internal consistency of KMD diagnosis, we created PI guidelines for QD, BD, YnD, and YgD with KM experts. Firstly, both conventional medicine and KM principles were considered. Secondly, the PI guideline was designed according to Donguibogam, KM textbook and results of a previous study. Thirdly, the PI guideline was modified to fit this study, which was based on the advice of the experts in this field. In addition, a modified PI guideline was revised through the consensus of the experts in this field. Based on the PI guidelines, three KMDs with 8 years of clinical experience independently will diagnose the participants’ deficiency PI status. Participants for which the KMD diagnoses disagreed will be excluded from analysis.

2.4. Measurements

2.4.1. Primary outcome
The QBYY-Q scores after two measurement sessions will be used as the primary endpoint. The QBYY-Q includes 32 questions, scored on a scale of 1–4, which will be used to evaluate the participant's qi, blood, yin, and yang deficiency level during Visit 2 and Visit 3.

2.4.2. Secondary outcome

2.4.2.1. CTIS. The CTIS consists of a lighting part, image acquisition part, tongue positioning part, data processing part, and a results display part. In particular, the software of CTIS was developed to analyze the CIE L*a*b* ([https://en.wikipedia.org/wiki/Lab_color_space](https://en.wikipedia.org/wiki/Lab_color_space)) of the tongue body and coating from the captured tongue image. The components and image analysis of CTIS were previously described in detail (Fig. 2).15

2.4.2.2. PI-Qs. This study uses three types of PI-Qs such as: (1) cold-heat; (2) food accumulation, and (3) seven emotions patterns. The validity and reliability of all PI questionnaires will be evaluated. The total score of each PI questionnaire will be calculated by summing up the items. A cold-heat PI-Q, consisting of 20 questions covering the following two categories, will be used to evaluate cold pattern and heat pattern. Each item is scored on a 7-point scale from 1 to 7.16 A food accumulation PI-Q consisting of 17 questions will assess the food accumulation. Each item is rated on a 7-point Likert scale: 1 = disagree very strongly; 2 = disagree strongly; 3 = disagree; 4 = neither agree nor disagree; 5 = agree; 6 = agree strongly; and 7 = agree very strongly.4 A seven emotions PI-Q, consisting of 18 items, will be used to evaluate seven emotions as follows: joy, anger, thought, anxiety, sorrow, fear, and fright.17

2.4.2.3. Fatigue questionnaires. To assess fatigue severity, a numerical rating scale will be used. The numerical rating scale scores are measured using the Korean-translated Chalder Fatigue Scale and the Fatigue Severity Scale, that enquires about the participant's current fatigue status.18,19 The Korean-translated Chalder Fatigue Scale comprises seven physical...
Table 1 – Study design schedule

| Period                        | Screening | Measurement 1 | Measurement 2 |
|-------------------------------|-----------|---------------|---------------|
| Informed consent             | •         |               |               |
| Inclusion and exclusion criteria | •       |               |               |
| Characteristics information  | •         |               |               |
| Vital signs                   | •         |               |               |
| Medical history               | •         |               |               |
| Diagnosis of PI              | •         |               |               |
| Diagnosis of chronic fatigue | •         |               |               |
| PSS                           | •         |               |               |
| QBYY-Q                        |           | •             | •             |
| PI-Q                          | •         | •             | •             |
| FSS                           | •         | •             | •             |
| CFS                           | •         | •             | •             |
| Laboratory test               | •         | •             | •             |
| Acquisition of tongue image  | •         | •             | •             |
| Patient’s compliance         | •         | •             | •             |
| Adverse event                 | •         | •             | •             |

※: Item has to be carried out for the visit in all participations.
(1) Check the inclusion and exclusion criteria; (2) characteristics information: age, sex, date of birth, smoking, alcohol, caffeine, disease history, surgery history, drug taking, menstrual period, etc.; (3) vital signs: height, weight, temperature, systolic and diastolic pressure; (4) diagnosis of following pattern identification of patients: qi deficiency, blood deficiency, yin Deficiency, and yang deficiency; (5) All laboratory test results should be interpreted within the normal reference values. Laboratory test: blood test (complete blood cell count, white blood cells, differential cell count, erythrocyte sedimentation rate, alkaline phosphatase, aspartate transaminase, alanine transaminase, protein, albumin, blood urea nitrogen, creatinine, gamma-glutamyl transferase, total bilirubin, direct bilirubin, uric acid, C-reactive protein, sodium, potassium, chloride, thyroid stimulating hormone) and urinalysis (pH, specific gravity, protein, glucose, ketone, bilirubin, urobilinogen, nitrite, urine micro red blood cells, white blood cells); (6) acquisition of tongue image by computerized tongue image analysis system; (7) check whether participation is enrolled or not by interview and case report form; and (8) medical examination by interview and self-report of adverse event.

CFS, chronic fatigue syndrome; FSS, Fatigue Severity Scale; PI, pattern identification; PI-Q, pattern identification questionnaires (cold-heat, food accumulation and seven emotions patterns); PSS, Perceived Stress Scale; QBYY-Q, Qi Blood Yin Yang deficiency questionnaire

2.5. Follow up

The follow-up assessment is designed to evaluate the test–retest reliability of QBYY-Q. Upon completion of the first measurement, follow-up assessments will be conducted after 3–5 weeks. In addition, patients will keep the precautions when attending this study and complete the QBYY-Q, PI-Q, and CTIS measurements in the follow-up period. Patients will send the relevant information to researchers immediately. To encourage participant compliance, we will show special solicitude for every participant and closely monitor the evolution of their illness. The measured QBYY-Q scores at Visit 2 and Visit 3 will be compared between the first measurement and second measurement.

2.6. Randomization and blinding

This is a nonrandomized and nonblinded study.

2.7. Safety monitoring

Possible adverse events (AEs) due to laboratory tests and tongue image acquisition include burns, electric shock, and infection. All unexpected and unintended responses will be reported as AEs by the researcher at every visit, even if they are not necessarily related to this study. The AEs will be carefully recorded in the case report form (CRF) by the corresponding research staff.

2.8. Quality control and monitoring

Sponsor monitoring will be performed by highly trained monitoring staff throughout the trial. All staff who sponsor, assistants, principal researcher, assessors, and coordinators must attend training to make sure all practices according to the standard operating procedures. In addition, all researchers must understand the purpose and process of this study. A sponsor will visit once-a-month to check the compliance with standard operating procedures regularly. Report of audits should be presented to the chief monitor.

2.9. Data management

No record can be missed or omitted in the original data source. Every correction should be explained in the appended notes, signed, and dated by the physicians participating
in the clinical trial; primary entries are not allowed to be changed. After the observation of a clinical case, CRF files will be submitted to the project directors for verification and signed by supervisors. Data input will be done separately by two data collectors with computers and locked once the checking work is done. The data manager will clarify all the questions regarding the CRF with the researchers through clinical supervisors. Researchers should answer all questions as soon as possible so that the data manager can conduct the modification, validation, and entry of the data.

2.10. Statistical analysis

Descriptive statistics will be performed using R software, version 3.1.1, on a Windows 7 platform (R Development Core Team. Auckland, New Zealand). The level of significance is set to \( p < 0.05 \) for all the analyses. An investigator will survey the demographic characteristics, UCF types, and deficiency types of UCF patients and controls. Statistics experts will analyze the relationship between results using the Pearson’s Chi-squared test and independent t-test in the R Statistics program.

2.11. Ethics

This study is conducted according to the Declaration of Helsinki 2008 and the regulations of the Good Clinical Practice principles in the Korea Food and Drug Administration. This protocol was reviewed and approved by the Institutional Review Board of the Won Kwang University, Gwangju Korean Medical Hospital in May 2015 (approval No. 2015/3) before the participant recruitment. This clinical study was registered on June 15, 2015 at the Korean Clinical Trials Registry with the identifier number KCT0001521. The study was conducted according to the principles of the Declaration of Helsinki.

3. Discussion

UCF is a major public health problem. To date, UCF remains unclear and has no quantitative diagnostic tools and specific treatment. KM has been widely considered an alternative option for chronic illness in East Asia. KM was more effective for chronic illness in East Asia. KM has been widely considered an alternative to conventional medicine in the treatment of UCF. Thence, conventional medicine can cause unwanted side effects, however, KM causes no serious side effects such as headaches, vomiting, fever, nervousness, spontaneous bleeding, and changes in appetite. According to KM, UCF is categorized into patterns of deficiency or excess. UCF is mainly diagnosed the deficiency pattern, classified into qi, blood, yin, and yang deficiencies, and specialized treatments are then applied according to the particular deficiency patterns. In general, PI diagnosis is a key tool of KM treatment and has great curative power for many chronic illness. However, no diagnostic tools, such as a questionnaires or medical devices, have been validated in clinical trials. Therefore, the current study was designed to obtain objective diagnostic tools on the usefulness of QBYY-Q for the diagnosis of four deficiency patterns in the UCF patients. The clinical trial protocol plays a vital role of study conduct, reporting, and appraisal. To facilitate appropriate high quality methodology and strict quality control, this protocol has been developed according to the previous protocol data and clinical data.

If the clinical effectiveness of QBYY-Q is verified in the present study, it will provide reasonable evidence for prescribing herbal medicine for UCF and related-UCF patients. It could be used as a new alternative diagnostic tool in patients with UCF, which is without established standard therapies in conventional medicine. The current study has two potential strengths. Firstly, it is unique and a first attempt. Secondly, we will determine whether the characteristics of the tongue can change QBYY-Q scores and the subjective feeling of fatigue. Although the relationship between a tongue diagnosis and PI or fatigue severity is controversial, the change in these factors associated with PI diagnosis could be compared in this study.

Firstly, our study will be conducted only in Gwangju, Korea and, as a result, has limited population validity. Secondly, this study has the possibility of a high risk of bias regarding diagnosed patients’ PI. These standards are different from the symptoms and signs of PI, which are very difficult to standardize. Further studies are considered to overcome these limitations with respect to population validity and standard guideline for diagnosis of PI. Large clinical trials in multiple centers on PI and the evaluation of the therapeutic effects on UCF in randomized clinical trials are also needed. It is believed that this study will provide a reference data and good evidence that are applicable to future studies. Moreover, the results of the present study can be used to improve the care of patients with UCF and UCF-related disorders and to facilitate research on anti-UCF therapies using KM. The trial is currently in the recruitment phase. Participant recruitment started in July 2015, and is expected to end in October 2015.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgments

We thank all of our colleagues who participated in this study. This study was supported by the Korea Institute of Oriental Medicine (K15011), Republic of Korea.

Appendix 1. Qi Blood Yin Yang deficiency questionnaire.

We would like to know more about any problems you have experienced recently. Please answer all the questions by checking the answer that applies to you most closely.

1: disagree strongly, 2: disagree, 3: agree, 4: agree strongly
| Condition                                                                 | 1 | 2 | 3 | 4 |
|--------------------------------------------------------------------------|---|---|---|---|
| I feel listless                                                          | ☐ | ☐ | ☐ | ☐ |
| I feel too languid to work                                               | ☐ | ☐ | ☐ | ☐ |
| I feel feeling of helplessness                                           | ☐ | ☐ | ☐ | ☐ |
| I attempt the impossible                                                | ☐ | ☐ | ☐ | ☐ |
| I do not gain weight despite eating fully                                | ☐ | ☐ | ☐ | ☐ |
| I feel giddy                                                             | ☐ | ☐ | ☐ | ☐ |
| My heart keeps pounding                                                  | ☐ | ☐ | ☐ | ☐ |
| I feel dull pain in my low back or knee                                  | ☐ | ☐ | ☐ | ☐ |
| I feel weak and cannot move around much                                  | ☐ | ☐ | ☐ | ☐ |
| I feel hot deep in the body, hand, and foot                              | ☐ | ☐ | ☐ | ☐ |
| I often have a cramp                                                     | ☐ | ☐ | ☐ | ☐ |
| I have a flush in the afternoon                                          | ☐ | ☐ | ☐ | ☐ |
| I have a pale complexion                                                | ☐ | ☐ | ☐ | ☐ |
| I have a rough skin                                                      | ☐ | ☐ | ☐ | ☐ |
| My hair is friable                                                       | ☐ | ☐ | ☐ | ☐ |
| I have a bad complexion of lips, lids, and nail                          | ☐ | ☐ | ☐ | ☐ |
| I have a dry and fatigue eyes                                            | ☐ | ☐ | ☐ | ☐ |
| I have a failure of eyesight                                             | ☐ | ☐ | ☐ | ☐ |
| I have a dry mouth                                                       | ☐ | ☐ | ☐ | ☐ |
| I haven’t had my appetite lately                                        | ☐ | ☐ | ☐ | ☐ |
| I have a fever in the afternoon                                          | ☐ | ☐ | ☐ | ☐ |
| I prefer warm thing to cold thing                                        | ☐ | ☐ | ☐ | ☐ |
| I prefer warm beverages to cold beverages                                | ☐ | ☐ | ☐ | ☐ |
| My hands and feet get cold                                               | ☐ | ☐ | ☐ | ☐ |
| I usually sweat a lot these days                                        | ☐ | ☐ | ☐ | ☐ |
| I sweat during sleep                                                     | ☐ | ☐ | ☐ | ☐ |
| The voice is getting smaller                                             | ☐ | ☐ | ☐ | ☐ |
| I frequently had a dream during sleep                                    | ☐ | ☐ | ☐ | ☐ |
| I urinate frequently during feel cold                                    | ☐ | ☐ | ☐ | ☐ |
| I have diarrhea in the dawn                                              | ☐ | ☐ | ☐ | ☐ |
| I have soft stools                                                       | ☐ | ☐ | ☐ | ☐ |
| I have s symptoms of proptosis and hysteroptosis                         | ☐ | ☐ | ☐ | ☐ |

REFERENCES

1. Jorgensen R. Chronic fatigue: an evolutionary concept analysis. J Adv Nurs 2008;63:199–207.