HEALTH RELATED QUALITY OF LIFE OUTCOME IN PATIENTS WITH CHRONIC HEPATITIS C, REVIEW CONCEPTUAL MODELS

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ABSTRACT

Chronic hepatitis C (CHC) and its treatment are associated with different patient-reported symptoms and impacts. This literature review intend to identify concepts raised by CHC patients related to symptoms, treatment effects, and evaluated integration of these concepts within patient-reported outcome (PRO) measures. Hence Health related quality of life (HRQOL) is increasingly used as an outcome in clinical trials, effectiveness research, and research on quality of care. Factors that have facilitated this increased usage include the accumulating evidence that measures of HRQOL are valid and reliable. The publication of several large clinical trials showing that these outcome measures are responsive to important clinical changes. In this article, we reviewed some conceptual multi-dimensional models of HCV quality of life patients. The content dimensions were fitted to the domains and treatment dimensions. This review identified several gaps in the literature relating to assessment of symptoms and outcomes reported as important by CHC patients. A lot more research is needed to make certain that CHC clinical trials evaluate concepts that are important to patients and include measures that have evidence supporting content validity and reliability.

KEYWORDS: Health related, Quality of life, Chronic Hepatitis C, Conceptual Model

INTRODUCTION

Hepatitis C virus (HCV) Infection is the greatest cause of liver disease around the world. The widespread of antibody to hepatitis C is estimated to be 1.8% in the general population of the United States, and approximately 4 million persons in the United States currently have chronic hepatitis C infection[1]. Some patients remain asymptomatic for long periods of time and may never develop progressive or symptomatic liver disease[2]. There is some disagreement as to the prognosis of patients with chronic hepatitis C. Some suggest that most patients with chronic hepatitis C will have a normal life span and not suffer consequences of this disease[3]. Moreover, patients with hepatitis C infection have a reduced health-related quality of life. Even patients without cirrhosis show reductions that manifest in both mental and physical HRQOL[4]. These lowering have been

pronounced to be clinically and socially relevant[5], and are comparable with or more severe than those for a symbolic sample of type II diabetics[6]. Although it seems that patients with chronic hepatitis C have reduced HRQOL, it is unsettled whether this is bring about by the disease or by its associated comorbidities. Patients with hepatitis C are more likely to be hypodermic drug users, to come from low socioeconomic status, and to have a history of blood transfusions[7]. Trying to address this issue, Some Studies adjusted for some comorbidities, whereas others excluded subjects who reported a background of drug use. Both negotiated that subjects with hepatitis C had reduced HRQOL. Inspectors had become interested in measuring HRQOL in HCV clinical trials, as consciousness grows of the HRQOL decrease from HCV and its clinical consequences. This recognition that the burden of HCV extends beyond its economic impact coincides with

recommendations by the National Institutes of Health to conduct studies that measure not only traditional biological outcomes in HCV, but also patient-oriented outcomes[8]. However, most clinicians are not versed in the interpretation of HRQOL in HCV, and patient-oriented outcomes such as HRQOL may fail to resonate with clinicians in the same way as traditional biological parameters. Failure to understand and interpret HRQOL data in HCV may lead to the myopic view that biological outcomes are of primary importance a view that likely underestimates the true burden of illness engendered by HCV.Despite this fact that the disconnection between the importance of measuring HRQOL in HCV and the importance of inability of clinicians to willingly explain HRQOL differences, it is crucial to demonstrate the clinical significance of HRQOL score differences by presenting them to changes in clinically familiar outcomes[9]. Being aware of the clinically differences in HRQOL, researchers and patients can better realize not only the overall health responsibility of HCV, but also the optimal tackle to managing HCV. Nonetheless, despite the increasing awareness of HRQOL in HCV, there has been no attempt to systematically review the HRQOL literature in HCV. Quality of life by showing its importance in clinical research as an outcome variable has become a significant measure in clinical research. By adaptation from a biomedical model of health to one that incorporates the social aspects of disease, clinicians and researchers dealing with chronic illness now incorporate quality of life measures into clinical practice and research[10]. Patients with Chronic HCV disease has shown a significant impact on the well-being of patients and contributes to the significant morbidity associated with these conditions[11]. In this article, we use the terms quality of life and health-related quality of life interchangeably and we provide a brief discussion of the history, development, disease-specific quality of life measurements. The aims, goals, and assumptions that have inspired the field of health-related quality of life measurement have had a profound impact on the current state of these tools and delineate the challenges for the future. Also we review a conceptual model, a taxonomy of patient outcomes, which categorizes measures of patient outcome according to the underlying health concepts they represent and proposes specific causal relationships between different health concepts. The first stage defined the conceptual model of HCV HRQL and

generated items to reflect this model. Themes reflecting the lived experience of HCV were established through literature review, specialist consultation, and particularly patient interviews. From patient interview syntax a bank of potential items for a pilot PROQOL instrument was extracted.

Research Background

Chronic infection with the hepatitis C virus (HCV) results in morbidity and mortality related to hepatic and extra-hepatic disease processes. An estimated 130 and 170 million people worldwide are HCV-seropositive. The blood-borne virus is transmitted by unsafe medical and drug injecting practices and sexually when mucosal integrity is breached[12]. In specific contexts, such as prisons[13], regions with high prevalence and insufficient prevention measures[14], and in HIV-seropositive men[1], the risk of transmission is increased. Patient-Reported Outcome (PRO) measures are important to evaluate the impact of chronic infection; eligibility and readiness for treatment; and assessment of HRQL during and post treatment. These measures ensure patient experiences and preferences are captured in order to discriminate between treatment options[15]. Since PRO measures provide insight into the patient's perspective there must be evidence that the measures reflect that perspective, this is content validity. Saffari et al., (2015) in an article regarded to measuring Health-Related Quality of Life among Iranian Patients with Chronic Hepatitis B Stated that: "There are only a few measures to assess quality of life among patients with liver disorders, they said that Significant correlations were found between HRQOL measures. Disease duration, disease stage, and serum aspartate aminotransferase differentiated patients. Factor analysis determined a seven factor solution that explained 70% of the total variance. The LDSI2.0 is an appropriate HRQOL scale for use among Iranian patients with chronic hepatitis B based on its solid psychometric properties in this population". Hajibeigi et al., (2009) held an investigation in adults with beta-thalassemia, they stated that their aim was to investigate the association of anxiety and depression symptoms with health related quality of life (HRQoL) and sleep quality, in representing the results they stated that Mental and physical quality of life scores were predicted by symptoms of depression and somatic comorbidities. Total sleep quality was predicted by anxiety symptoms and somatic comorbidities. Asadi Noughabi et al.,

(2007) assessed the effect of education on Quality of Life in Patients under P-D Feron Treatment and in terms of results they stated that Planning short and simple educational programs has a significant effect on the patient's control on his/her disease and its' side effects; and can improve quality of life, life satisfaction feeling, and coping with treatment in patients with viral hepatitis. Zandi et al., (2005) assessed the effect of Self Care Program on Quality of Life in Patients with Cirrhosis referred to Tehran Hepatitis Center they stated that Liver cirrhosis is one of the most essential problems of health care system in the country, because of its high prevalence and it's disabling or deathly complications. Designing a self-care program according to client's needs in different aspects of quality of life, can maintain their independence, promote their sense of well-being and improve their quality of life. Finally the result of the present study confirmed the positive effects of the educational and self-care programs on the Quality of life of cirrhotic patients. Extensive educational and self-care programs along with long-term follow up such as the program conducted in this study are suggested. Azarkeivan et al., (2009) evaluate the Association of poor physical and mental health-related quality of life in beta thalassemia and stated that Using two logistic regression models, we determined the associates of poor physical and mental health related quality of life (HRQoL) among beta thalassemia patients. Finally they concluded that Depression is associated with both poor physical and mental HRQoL among patients

with major/ intermediate beta thalassemia, however somatic comorbidities and anxiety are associated with poor physical and mental HRQoL, respectively. Ghanbari et al., (2010) studied the life quality in patients with Hepatitis C and its comparison with healthy people and present a structural model, they stated that Hepatitis C is an asymptomatic disease. The quality of life is a major concern in these patients. And their study showed that hepatitis C is responsible for great alterations in HRQOL. Every effort is to be made to provide structural models in prediction of quality of life that would play a significant role in resolving of problems.

Health-related quality of life (HRQOL)
In the last two decades Measurement of HRQoL has become frequent as an outcome in clinical research. The use of instruments that range from general measures of well-being to more finite, disease specific measures has become commonplace, especially in assessing the efficacy of new interventions in clinical trials. Over five million individuals in the United States are affected by chronic liver diseases, and the impact of these diseases on patient well-being has become an important topic of research[16]. The concept of quality of life is not homogeneous as the terminology describes, and researchers use various terms interchangeably. Although these terms are often used to mean similar things, there are actually differences among them (Fig. 1).

Figure 1
Diagram of health-related quality of life.

Connecting variables by Models of Patient Outcomes

Implicit In the use of measures of HRQOL in clinical trials and in effectiveness research is the

concept that clinical interventions such as pharmacologic therapies can affect parameters such as physical function, social function, or mental health[8]. However, a clear understanding of these causal relationships will facilitate the design of optimally effective clinical interventions. The social science paradigm, or the quality of life model, focuses on dimensions of functioning and overall well-being, and current research examines ways to accurately measure complex behaviors and feelings. Experimental research designs are rarely possible since the focus of social science is on the way numerous social structures and institutions influence individuals[17]. These models of health have their foundations in sociology, psychology, and economics and use concepts and methodologies often foreign to physicians and clinical researchers. Researchers have proposed a number of conceptual models of the relationships among the components of HRQOL. The development of several of these models was prompted by the observation that commonly used measures of functional status frequently include conceptually distinct constructs of disease, functional limitations, and self-rated health[18]. However, none of these models include the full range of variables that now typically are included in HRQOL assessments[19]. Although some modeling work has been done, the principal goal of the field has been to validly and comprehensively describe health status.

First Model

For a good example of this, the PRO Concept Search identified 22 CHC-related concepts mentioned in three or more articles (Figure 2), Concepts included symptoms and treatment effects related to mental health, physical health, pain, HRQL, activities of daily living (ADL), cognitive dysfunction, and other categories[20]. The most frequently reported CHC-related concepts were: depression, fatigue, anxiety/fear, musculoskeletal pain/myalgia, flu-like symptoms, irritability, insomnia or sleep problems, and loss of appetite /anorexia/ weight loss, social functioning /isolation/stigma, gastrointestinal symptoms, reduced HRQL, cognitive impairment, and headache. The most commonly reported symptoms were: fatigue, depression, anxiety/fear, and inability to function or social consequences of disease. Other outcomes, including HCV symptoms and side effects of treatment, were: cognitive dysfunction, musculoskeletal pain, gastrointestinal symptoms, flu-like symptoms, dyspnea, headache, reduced functional capacity, reduced quality of life, insomnia or sleep problems, reduced sexual desire, and loss of appetite, weight loss or anorexia and the most frequently mentioned impact was on social function, including reduction in social activities, loss of social support, erosion of social roles, and HCV-related shame[21]. Psychological consequences were discussed along with a range of emotions, including grief, guilt, frustration, shame, shock, denial, despair, embarrassment, irritability, and hostility or anger[22]. Other emergent themes included difficulty at work, uncertainty or a lack of knowledge about the virus, issues related to stigma, and discussion of treatment costs and benefits[22]. Finally the overall list of concepts was evaluated based on ease of implementation into a clinical trial, potential to detect change over time in a clinical trial, how frequently the concepts appeared in the literature, how often the concepts were a primary focus of an article, and whether the concepts were independent or part of a larger group of concepts.
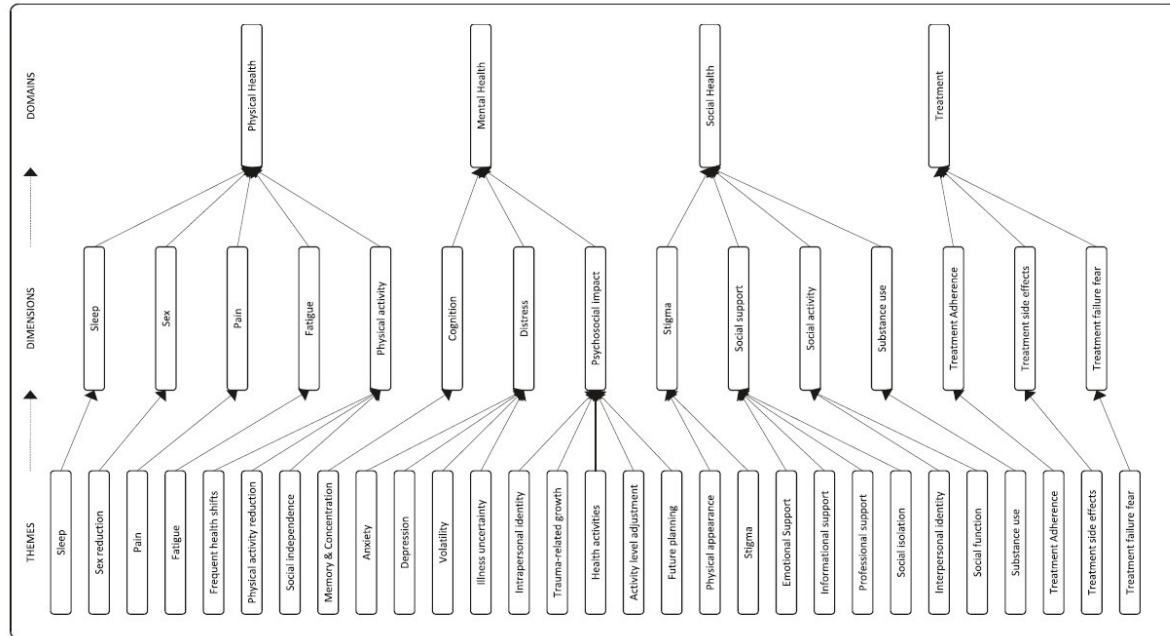

CHC PRO Concept Search –Concept List

Depression/suicidal tendencies
Fatigue/malaise/energy level
Anxiety/fear
Musculoskeletal pain/myalgia
Flu-like symptoms
Irritability
Insomnia or sleep problems
Loss of appetite/anorexia/weight loss
Social functioning/isolation/stigma
Abdominal pain/nausea/vomiting/diarrhea
Reduced health-related quality of life
Cognitive dysfunction
Headache
Mental health -anger/ hostility /aggression
Reduced functional capacity/physical and motor function
Dermatological problems
ADL and work impact, including loss of interest
Mental health -mania/hypomania
Dyspnea
Mental health -psychosis/other psychiatric disorders
Weakness
Sexual side effects

Figure 2
Pro Concept Search for Chronic hepatitis C

Second Model

In the following we review a conceptual model, according to analysis of interview, data revealed 29 themes constituting hepatitis C-specific HRQOL in the context of both chronic infection and treatment conditions. These were divide up into 15 dimensions showing the three overarching domains of Physical, Mental, and Social Health related quality of life, and finally HCV Treatment. These themes, dimensions and domains constitute the conceptual model of HCV HRQL, and coincide with holding HRQL theory. (Figure. 3)[18].

Figure 3
Conceptual Model of HCV specific HRQOL

The impact of some dimensions extended beyond their primary domains to affect others including sleep and sexual function, concentration, memory and treatment burden. Physical Health incorporated fatigue, pain, sleep and sexual impairment and physical activity; Mental Health included psychological distress, psychosocial impact, and cognition; Social Health incorporated support, activity, stigma, and substance use[22]. Treatment had influence on aspects of the three other domains with respect to treatment adherence, side effects, and treatment failure fears.

Physical domains of Health-related quality of life

Pain was proved by musculoskeletal discomfort, morning stiffness, and 'all over pain'. The pain dimension included themes of pain intensity and frequency and the extent it interfered with physical, mental and social activities. Fatigue was framed by disrupted physical, mental and social activity. Questionnaires described chronic low to medium intensity fatigue with debilitating, sporadic high intensity episodes typically occurring after injection of interferon. Physical activity was constrained by

health fluctuations that disrupted routines and planned activities. The need for rest limited mobility and travel distances and resulted in a greater reliance on others, especially family members, to carry out daily tasks. It was perceived that partners underappreciated the intensity of fatigue[23]. A waning capacity for activity was accompanied by a diminution of interests. The sleep dimension incorporated difficulties falling or remaining asleep, and disturbances arising from anxiety, pain and itching which effected alertness the next day. Depressive and treatment-related symptoms and contagion/transmission anxieties resulted in negative impacts on sexuality, including reduced libido, difficulty maintaining arousal and achieving orgasm.

Mental domains of Health-related quality of life

Antiviral treatment associated with depression, anxiety, stress and struggles led to distress. Feelings of nervousness, heightened irritability, anger and rage were disturbing and unexpected. Questionnaires described shock, disbelief, grief, frustration, and helplessness. And the participants

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were concerned their infections might be inveterate and felt a loss of control and independence. Some viewed their futures to be bleak and in some cases were fearful of dying; and emotional distress disrupted relationships[8]. Mental health-related changes resulted in an altered self-perception and expression of personality. Psychosocial impacts were described that reflecting adaptations to HCV associated emotional reactions. Admiration of life was re-appraised and goals adjusted, and some described a greater respect and empathy for others. Behavioral changes in health-seeking practices were related to diet, exercise, usage of complementary therapies and altered hygiene routines. Cognitive and behavioral strategies included: positive thinking, for example, that side effects of medication were part of the healing process, determination to complete the treatment course, meditation and prayer. Difficulties with congregation and memory interfered with maintaining schedules, locating essential tools and completing sequential steps in a task. Cognition was disrupted by sleep disturbances and fatigue.

Social domains of Health-related quality of life
Questionnaires described losing social invitations, companionship and marital/ relational instability but others described feeling cared for and valued. Surrounded by the sense of being cared for by relatives and friends; and professional and informational support. Normal association with health professionals supported confidence, sense of control and medication adherence. Loss of social activity drew together, thematically, the interest, accessibility, capacity and satisfaction with typical daily social activity following a diagnosis of HCV. HCV-related shame infused the Social Health-related quality of life domain and influenced personal and social identity. Occasions to engage in group exercising activities due to infectivity, and avoidance of drugs and alcohol, limited social interaction as did limited energy and a sense of lost attractiveness. Self was perceived as 'diseased' and there was a fear of disclosing HCV serostatus and transferring the infection. Hence, differentiation in healthcare settings, the office, and from relatives and friends was evidenced. Shame concerns often resulted in socially avoidant behavior. The use of substances was characterized by positive and negative statements related to coping with reduced substance use leading to better health but also the loss of socialization with friends connected through

the use of drugs and alcohol[12]. Some failed to cope with the abstinence required for treatment eligibility and struggled to overcome substance dependency.
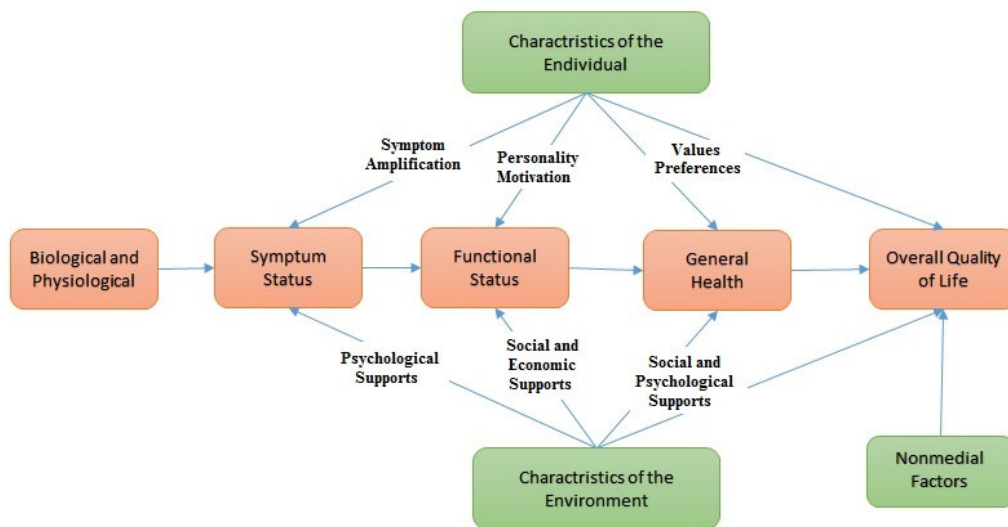
Treatment
Participants undergoing hepatitis treatment were required to make life adjustments for the duration of therapy. Treatment will impact the other domains of HRQL in complex ways[24]. Regimen adherence was described as a 'responsibility' which restricted travel and required concealment. Prior to treatment there was fear of side effects and treatment inefficacy. Side-effects including changes in appearance like weight loss, jaundice and hair loss affected self-esteem and sense of social acceptability sometimes resulting in treatment cessation (or interruption). Participants also felt ready to manage and some with the means to do so, made plans to abolish socially and/or from employment to complete treatment. Determination was evident with hopes of longevity promoting persistence with treatment, others were anxious about treatment failure or recurrent infection. Side effects that impacted mood were troublesome, including aggression and irritability, sexual function, personal appearance and interruptions to travel plans.

Third Model
The concept of quality of life is distinct from health, though related to it[25]. Economic, political, cultural, and spiritual factors may affect overall quality of life, but are generally not considered to fall under the purview of physicians and health care systems. Clinicians and clinical researchers are usually interested in HRQOL, or the aspects of quality of life that relate specifically to a person's health5. Health status and HRQOL can refer to different concepts[26], but in this article we use the terms interchangeably. Most conceptualizations of HRQOL include the dimensions of physical functioning, social functioning, role functioning, mental health, and general health perceptions[27], with important concepts such as vitality (energy/fatigue), pain, and cognitive functioning subsumed under these broader categories. Clinical data, such as measures of biological and physiological function, tissue diagnoses, and patient reported symptoms, are only occasionally included in conceptualizations of HRQOL[28]. Measures of health can be thought of as existing on a continuum

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of increasing biological, social, and psychological complexity. At one end of the continuum are biological measures, and at the other are more complex and integrated measures such as physical functioning and general health perceptions. These relationships, are displayed schematically in the Figure and described in detail herein. The arrows in the Figure do not imply that there are not reciprocal relationships. Neither does the absence of arrows be- tween nonadjacent levels imply that there are not such relationships. The main purpose of the Figure is to distinguish among conceptually distinct measures of HRQOL and to make explicit what we think are the dominant causal associations. The

following five subsections of the paper will describe each of the five levels in the model: biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life. Included in each will be a description of the health concepts represented by each level and a justification for their inclusion, a description of what is known about the relationships of concepts at that level to levels preceding it in the model. Because the relationship of emotional or psychological factors to each of the levels in the model is quite important, particularly complex, and not fully shown in the figure.

Figure 4
Relationship among measures of Patient outcome in a Health-related quality of life conceptual model

Biological and Physiological Factors
The most fundamental determinants of health status are molecular and genetic factors, but we begin our model with biological and physiological factors because these are commonly conceptualized, measured, and applied in routine clinical practice. The assessment of biological and physiological factors focuses on the function of cells, organs, and organ systems. Examples include the following: diagnoses such as pulmonary tuberculosis, inflammatory bowel disease, or small cell lung cancer; laboratory values such as serum hemoglobin or creatinine; measures of physiological function such as pulmonary function tests; and physical examination findings such as a systolic ejection murmur, pulmonary wheezes, or splenomegaly. Also included at this level in the model are factors whose effects on health are

principally mediated by changes in cell, organ, or organ system function.

Symptoms
When symptoms are assessed, the focus shifts from specific cells and organs to the organism as a whole. Several different classes of symptoms have been described. Physical symptoms have been defined as a perception, feeling or even belief about the state of the body[18] (Van der Plas et al, 2004). Psychophysical symptoms have been referred to as symptoms primarily associated with mental health or symptoms not clearly physical or psychological in origin. Less clearly conceptualized are emotional or psychological symptoms such as fear, worry, and frustration. Emotions and physical symptoms tend to be related when studied empirically, and causal relationships clearly can go in both directions[29]. Symptom reports, are expressions of subjective

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experiences that summarize and integrate data from a variety of disparate sources[18]. Patient-reported symptoms not only cause patients to enter the medical system, they also may affect subsequent use and the costs of medical care. Given that biological and physiological factors have an inconsistent relationship to symptoms, it is unlikely that treatments directed at biological and physiological factors alone, even if they can be identified, will be fully effective in the relief of symptoms. Research that explores other likely determinants of patient reported symptoms such as psychological factors, patient expectations, social factors, and aspects of the physician patient relationship may help clinicians to address better both the clinical and nonclinical factors related to reported symptoms[29].

Functioning

The next level in the model is functional status, and like symptom status, it is an important point of integration. Measures of function assess the ability of the individual to perform particular defined tasks. Symptom status is one important determinant of functioning. Other patient specific factors will also be important, such as personality and motivation[10]. Given two older women with similar hip conditions, the one who is more determined to be self-sufficient may function at a higher level. Many aspects of an individual's social environment also may have an important effect on functioning. In a clinical trial comparing oral and injectable gold with placebo in patients with rheumatoid arthritis the relationships of several physical examination findings to functioning were examined. There were significant correlations between change scores of joint tenderness, joint swelling, and grip strength and a measure of physical function, but not between change scores of these three clinical variables and psychological function[30].

General Health Perceptions

Two salient characteristics of general health perceptions are that they represent an integration of all of the health concepts that we have previously dis- cussed, as well as others such as mental health, and they are by definition a subjective rating. This and related concepts have been reviewed in detail recently[30]. The importance of general health perceptions arises from the observation that they are among the best predictors of the use of general medical and mental health services as well as

strong predictors of mortality, even after controlling for clinical factors[10].

Overall Quality of Life

Researchers frequently assess respondents' subjective well-being with general measures of how happy and/or satisfied they are with their life as a whole. Numerous typologies of well-being constructs and theories of subjective well-being have been developed and tested[10]. Review of these theories is beyond the scope of this article, but in most theories these measures are assumed to represent a stable synthesis of a wide range of experiences and feelings that people have[13].

The Role of Patient Preferences

Patients' preferences or values play an important role at several points in the model and are particularly important in understanding the last two levels in the model-general health perceptions and overall quality of life. For any individual, certain symptoms are more burdensome than others, and those individuals will prefer not to have those symptoms even if they may have to put up with others. For example, in a study of patients undergoing prostatectomy, it was found that among patients with severe symptoms, 32% reported no day to day limitations because of their prostate condition, and 19% reported no worry about their health because of their prostate. Among patients who had already had an episode of acute retention, 47% reported no day to day limitations, 19% no discomfort from the prostate, and 42% no worry about health because of their prostate. Among older men with similar prostate symptomatology, both levels of worry and limitations because of their prostate condition varied considerably, presumably because each patient valued these symptoms differently. This finding has important implications for treatment[28].

The Role of Emotional or Psychological Factors in the Model

The distinction between a physical symptom and physical function is relatively clear. Hip pain in an elderly woman is a symptom, and the inability to walk up stairs is an impairment of function. Although it certainly is the case that patients who attempt to do more experience more pain, it is likely that the more consequential causal pathway is that the pain is causing the functional impairment. Using similar logic, a psychological symptom is a

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feeling such as depression or anxiety, and impairment of psychological functioning would be the inability to accomplish a task that requires psychological health such as making difficult decisions or handling stressful situations. However, many scales that measure mental health or psychological well-being actually assess symptoms of emotional or psychological distress, not how these symptoms impair the performance of particular tasks. An emotional or psychological factor such as depression could be classified three different ways. Some would argue that depression has a strong biological component and would, there- fore, classify it as a biological or physiological factor. A scale that specifically assessed emotional symptoms associated with depression might classify depression as a measure of symptom status. Finally, a scale that focused on the behavioral impairment associated with depression might classify it as a measure of psychological functioning. Regardless of how emotional or psychological factors are classified, these factor scan have causal relationships with variables at every level of the model, although they are not represented in the Figure. Furthermore, most of these relationships can be bidirectional. Consider the case of a Hepatitis with depression. Depression may cause serum glucose to rise if it makes the patient unable or unwilling to comply with an effective finger stick and insulin regimen. Finally, the effect of depression on general health perceptions and overall quality of life can be profound. Similar arguments can be made for other psychological symptoms such as anxiety, fear, and hopelessness. Reasoning in the opposite direction, worsening physical symptoms, functional impairments, and low overall quality of life all can cause depression, anxiety, and fear. Measures of psychological health and many other measures of patient outcome are empirically related to each other, defying simple unidirectional models of causation. Pain can cause depression, and that depression can worsen pain. Further, treatment of each can improve the other. Therefore, the causal relationships between emotional or psychological phenomena and many of the other factors in the model should be considered potentially bidirectional. We think this issue is most salient for emotional and psychological factors, but it also is relevant for the other associations in the model. As mentioned in the introduction, the arrows in the Figure identify what we hypothesize are the

dominant associations; there also may be reciprocal associations in many cases.

CONCLUSION

Chronic hepatitis C and its treatment are associated with a wide variety of symptoms and impacts as reported by patients. The concept of quality of life has been through a transition, moving from measurement of a strictly physical state of health to encompassing the psychosocial aspects of disease. It is now commonplace for clinicians and investigators studying chronic illness to use quality of life instruments in their research. The research on patients with chronic liver disease shows us that these individuals experience significant impairments in their health-related quality of life. As clinicians continue to incorporate health-related quality of life measures into their practice, they will be able to develop treatment strategies in a patient-oriented manner. Presented models proposes a taxonomy or classification scheme for different measures of health outcome. The model and instrument incorporate three broad HRQL domains of Physical, Mental and Social Health, and-Treatment- that captures patient experience with interferon-based and interferon free regimens. The model and pilot instrument embody the breadth of issues impacting the quality of life of people affected by hepatitis C and clearly demonstrate content validity. Other HRQL instruments identify and elucidate one or more of these themes, but do not unify them within a comprehensive HCV-specific HRQL model. The conceptual model incorporates the impact of treatment into HRQL assessment. This is novel. This instrument was developed in the context of chronic infection, HIV co-infection and changing treatment strategies. Identifying fluctuation or changes in HRQL in response to interventions is critical to effective monitoring of patient outcomes and PRO QOL HCV captures these nuances. However, mathematical modelling suggests that HCV is underdiagnosed, people with existing infections are numerous and that better clinical management of infected people is required. Given the evident HRQL impacts of HCV we recommend embedding monitoring of patient-reported outcomes in clinical care. PRO QOL HCV, derived from the HCV-specific conceptual model, shows promise as a comprehensive and discriminating PRO instrument sensitive to the full range of disease and treatment

experiences of HCV patients, clearly distinguishing it from existing HRQL measures. In the third model, the concepts at each level are increasingly integrated and increasingly difficult to define and measure. At each level, there are an increasing number of inputs that cannot be controlled by clinicians or the health care system as it is traditionally defined.

REFERENCES

1. Kwan JW, Cronkite RC, Yiu A, Goldstein MK, Kazis L, Cheung RC. The impact of chronic hepatitis C and co-morbid illnesses on health-related quality of life. Quality of Life Research. 2008 Jun 1; 17(5):715-24.
2. Borgaonkar MR, Irvine EJ. Quality of life measurement in gastrointestinal and liver disorders. Gut. 2000 Sep 1; 47(3):444-54.
3. Dalgard O, Egeland A, Skaug K, Vilimas K, Steen T. Health□related quality of life in active injecting drug users with and without chronic hepatitis C virus infection. Hepatology. 2004 Jan 1; 39(1):74-80.
4. Helbling B, Overbeck K, Gonvers JJ, Malinverni R, Dufour JF, Borovicka J, Heim M, Cerny A, Negro F, Bucher S, Rickenbach M. Host-rather than virus-related factors reduce health-related quality of life in hepatitis C virus infection. Gut. 2008 Nov 1; 57(11):1597-603.
5. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology. 2005 Apr 1; 41(4):790-800.
6. Kasper DL, Fauci AS. Harrison's infectious diseases. McGraw-Hill; 2013.
7. Pojoga C, Dumitrascu DL, Pascu O, Grigorescu M, Radu C, Damian D. Impaired health-related quality of life in Romanian patients with chronic viral hepatitis before antiviral therapy. European journal of gastroenterology & hepatology. 2004 Jan 1; 16(1):27-31.
8. Younossi Z, Henry L. Systematic review: patient□reported outcomes in chronic hepatitis C□the impact of liver disease and new treatment regimens. Alimentary pharmacology & therapeutics. 2015 Mar 1; 41(6):497-520.
9. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr 1; 49(4):1335-74.
10. Chang SC, Yang SS, Chang CC, Lin CC, Chung YC, Li TC. Assessment of health-related quality of life in antiviral-treated Taiwanese chronic hepatitis C patients using SF-36 and CLDQ. Health and quality of life outcomes. 2014 Jun 18; 12(1):97.
11. Zhuang G, Zhang M, Liu Y, Guo Y, Wu Q, Zhou K, Ji Z, Zhang X. Significant impairment of health-related quality of life in mainland Chinese patients with chronic hepatitis B: a cross-sectional survey with pair-matched healthy controls. Health and quality of life outcomes. 2014 Jun 14; 12(1):101.
12. Teuber G, Schäfer A, Rimpel J, Paul K, Keicher C, Scheurlen M, Zeuzem S, Kraus MR. Deterioration of health-related quality of life and fatigue in patients with chronic hepatitis C: Association with demographic factors, inflammatory activity, and degree of fibrosis. Journal of hepatology. 2008 Dec 31;49(6):923-9.
13. Farivar SS, Cunningham WE, Hays RD. Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey, V. 1. Health and quality of life outcomes. 2007 Sep 7; 5(1):54.
14. Thomas DL. Global control of hepatitis C: where challenge meets opportunity. Nature medicine. 2013 Jul 1; 19(7):850-8.
15. Kleinman L, Mannix S, Yuan Y, Kummer S, L'Italien G, Revicki D. Review of patient-reported outcome measures in chronic hepatitis C. Health and quality of life outcomes. 2012 Aug 7; 10(1):92.
16. Adler N, Stewart J, with the Psychosocial Research Group. The MacArthur Scale of Subjective Social Status. 2007.
17. Dan AA, Martin LM, Crone C, Ong JP, Farmer DW, Wise T, Robbins SC, Younossi ZM. Depression, anemia and health-related quality of life in chronic hepatitis C. Journal of hepatology. 2006 Mar 31; 44(3):491-8.

18. Van der Plas SM, Hansen BE, Boer JBD, Stijnen T, Passchier J, Man RAD, et al. The Liver Disease Symptom Index 2.0; Validation of a disease-specific questionnaire. Qual Life Res. 2004; 13:1469–81.

19. Lohr KN. Assessing health status and quality-of-life instruments: attributes and review criteria. Quality of Life Research. 2002 May 1; 11(3):193-205.

20. Thomas DL. Cure of hepatitis C virus infection without interferon alfa: scientific basis and current clinical evidence. Topics in antiviral medicine. 2014; 21(5):152-6.

21. Gutteling JJ, De Man RA, Van Der Plas SM, Schalm SW, Busschbach JJ, DARLINGTON AS. Determinants of quality of life in chronic liver patients. Alimentary pharmacology & therapeutics. 2006 Jun 1; 23(11):1629-35.

22. Fayers PM, Machin D. Quality of life: the assessment, analysis and interpretation of patient-reported outcomes. John Wiley & Sons; 2013 May 23.

23. Younossi Z, Henry L. The impact of the new antiviral regimens on patient reported outcomes and health economics of patients with chronic hepatitis C. Digestive and Liver Disease. 2014 Dec 15; 46:S186-96.

24. Higgs P, Wright C, Hellard M. new treatments for hepatitis C have implications for quality of life in people who inject drugs. Alimentary pharmacology & therapeutics. 2016 Apr 1; 43(7):840-1.

25. Ong SC, Mak B, Aung MO, Li S, Lim S. Health-related quality of life in chronic hepatitis B patients. HEPATOLOGY. 2008; 47(4):1108–17. doi: 10.1002/hep.22138. Pmid: 18318043.

26. Lam ET, Lam CL, Lai CL, Yuen MF, Fong DY, So TM. Health-related quality of life of Southern Chinese with chronic hepatitis B infection. Health and quality of life outcomes. 2009 Jun 5; 7(1):52.

27. Trembling PM, Tanwar S, Dusheiko GM. Protease inhibitors for chronic hepatitis C: Management of side effects. Hot Topics in Viral Hepatitis 2012; 25:19–26.

28. Gralnek IM, Hays RD, Kilbourne A, Rosen HR, Keeffe EB, Artinian L, Kim S, Lazarovici D, Jensen DM, Busuttil RW, Martin P. Development and evaluation of the liver disease quality of life instrument in persons with advanced, chronic liver disease—the LDQOL 1.0. The American journal of gastroenterology. 2000 Dec 1; 95(12):3552-65.

29. Justice AC, Holmes W, Gifford AL, Rabeneck L, Zackin R, Sinclair G, Weissman S, Neidig J, Marcus C, Chesney M, Cohn SE. Development and validation of a self-completed HIV symptom index. Journal of Clinical Epidemiology. 2001 Dec 31; 54(12):S77-90.

30. Björnsson E, Verbaan H, Oksanen A, Frydén A, Johansson J, Friberg S, Dalgård O, Kalaitzakis E. Health-related quality of life in patients with different stages of liver disease induced by hepatitis C. Scandinavian journal of gastroenterology. 2009 Jan 1; 44(7):878-87.

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