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Pilot Randomized Controlled Trial of Laparoscopic Cholecystectomy vs Active Non-operative Therapy for the Treatment of Biliary Dyskinesia

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Abstract

Introduction—Despite widespread adoption by the surgical community, high-quality prospective data supporting the practice of laparoscopic cholecystectomy (LC) for the treatment of biliary dyskinesia (BD) is lacking.

Methods—Adult patients meeting criteria for diagnosis of BD (Rome III symptoms, normal ultrasound, gallbladder ejection fraction <38%) were randomized to either LC or a trial of non-operative (NO) therapy with a low-dose neuromodulator (amitriptyline 25mg/day). Patients in the NO arm were allowed to cross over to the surgical arm and remain in the study for any reason. Besides collection of basic demographics and medical/surgical history, patients were administered a standardized quality of life (QOL) assessment (SF-8) and a symptom-specific questionnaire (Rome III criteria) at enrollment and monthly through the study to assess the effect of treatment on biliary symptoms and overall QOL.

Results—Thirty patients were enrolled over 12 months (15LC, 15NO). In the LC group, 13 underwent LC, 1 refused surgery, 1 withdrew. In the NO group, 14 crossed over to the LC group (of which 13 had LC), yielding 26 patients who underwent LC. SF-8 physical scores (PCS-8) were significantly improved at both the first and last follow-up visits ($p < 0.0001$, $p = 0.0003$ respectively). SF-8 mental scores (MCS-8) were also significantly improved at both the first and last follow-up visits ($p = 0.0187$, $p = 0.0017$ respectively). With median follow-up of 12 months [range 3–14], all 26 reported relief of pain.

Conclusions—This pilot study raises doubts regarding the feasibility of a randomized trial, presumably due to both clinician and patient bias toward LC and the lack of “gold-standard” non-

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operative treatments. However, these prospective data indicate that, with careful patient selection (standardized symptom criteria/imaging methodology), LC results in pain relief and significant improvement in QOL in BD patients. Further prospective study of these findings is warranted.

Introduction

Biliary dyskinesia (BD) is a disorder characterized by the presence of biliary symptoms, a sonographically normal gallbladder, and an abnormally low gallbladder ejection fraction (GBEF) diagnosed by an abnormal cholecystokinin-cholescintigram (CCK-HIDA scan) ¹. Although laparoscopic cholecystectomy (LC) has been widely adopted as the preferred treatment for biliary dyskinesia¹, this practice remains controversial owing to a lack of high-quality prospective data supporting the practice ^{2,3,4,5}. To date, only one randomized controlled trial examining the role of cholecystectomy for BD has been published. This study, conducted by Yap et al. and published in 1991 consisted of only 21 patients ⁶. Since then, all published data on this subject has been in the form of retrospective case series, systematic reviews, and meta-analyses, and these have varied widely in terms of inclusion/symptom criteria, technique of biliary imaging and GBEF determination, definition of what constitutes a successful treatment, and duration of follow up ⁷. Although the need for additional randomized controlled trials examining the role of LC for the treatment of BD has been acknowledged by the majority of authors to be needed, none have been conducted prior to the results reported in this manuscript.

The following study describes the results of a novel randomized controlled pilot study examining the role of LC vs. a regimen of active non-operative (NO) medical therapy in the treatment of BD, focusing on both the feasibility of such a trial and the results of the prescribed treatments.

Patient population and methods

The study design was that of a pilot randomized controlled trial involving two treatments for patients with a diagnosis of biliary dyskinesia. These treatments included laparoscopic cholecystectomy (LC) – the current standard of care for treatment of BD, and an active non-operative (NO) treatment group which consisted of maintenance of a low-fat diet and treatment with a low dose neuromodulator – amitriptyline 25mg orally once daily. This medication was chosen for its success in the treatment of chronic pain and other functional gastrointestinal disorders ⁸. This choice was also felt to be superior than the alternative of simply providing a placebo, since we found in exploratory studies at our institution that patients in pain were not willing to be randomized to a treatment arm with a drug of which they had no knowledge of, rather than one with at least some available data suggesting its effectiveness.

The study was conducted over an 18 month period, of which the first enrollment was allowed within the first 12 months, thus ensuring a minimum follow up of 6 months for all patients, and potentially 18 months follow up for the first patient enrolled. Eligibility for enrollment was limited to patients 18 years of age and older with a normal gallbladder ultrasound, symptoms compatible with gallbladder dyskinesia as defined by the Rome III

criteria⁹, and a CCK-HIDA scan with a GBEF of <38% that was performed using updated Society of Nuclear Medicine (SNM) guidelines for test administration and GBEF calculation^{10,11}. Specifically, this consisted of a weight-based infusion of cholecystokinin (CCK, 0.02 mcg/kg) infused over one hour, with the GBEF calculated at the one hour mark^{10,11}. Patients were excluded from enrollment if they had chronic abdominal pain from a secondary diagnosis (such as Crohn's disease, peptic ulcer disease, or pain responsive to antacid/anti-secretory therapy), a history of allergy to amitriptyline or any comorbid condition that contraindicated its usage, or atypical symptoms not consistent with that described by the Rome III criteria. Patients with gallstone disease were excluded as well. Also, patients with a history of chronic narcotic use were also excluded as this negatively affects reliability and reproducibility of the CCK-HIDA results¹¹. No power calculation was performed as this was a pilot study.

The study protocol was approved by the Charleston Area Medical Center/WVU Charleston Division Institutional Review Board. Funding for the project was provided by the West Virginia Clinical and Translational Science Institute, NIH grant U54GM104942. After approval, a management algorithm was used to implement the protocol. The Center for Health Services and Outcomes Research served as the independent safety and monitoring board throughout the duration of the study in conjunction with the Charleston Area Medical center Clinical Trials Center.

Data Collection

Following informed consent, the following information was obtained by the study coordinator. Baseline data included demographic data (age, race, gender), SF-8 assessment as a valid measure of symptom severity and overall quality of life, complete medical history, medication and surgical history, and complete assessment of patient symptoms including a review of disease specific symptoms against the Rome III criteria for functional gallbladder disorder. (Table 1) Ultrasounds were reviewed on all patients to verify the presence of a sonographically normal gallbladder, as were the CCK-HIDA scans to verify that the appropriate SNM technique was used to perform the study. Data regarding reproduction of symptoms during performance of the CCK-HIDA scan were not collected, since these have been shown to have no consistent predictive value with respect to relief of biliary pain with cholecystectomy².

Patients meeting inclusion criteria were then randomized to either the surgical (LC) or active non-operative therapy (NO) group. Patients in the surgery arm were scheduled for LC immediately and followed throughout the remainder of the 18 month study period. Patients randomized to the NO arm received a prescription for amitriptyline and were educated on how to follow a low-fat diet. In addition, patients randomized to the NO management arm were asked to maintain a food diary and a symptom diary as well as document any side effects pertaining to the medication amitriptyline. All patients, regardless of their assigned treatment arm, received a monthly phone call for assessment of their condition. Formal symptom assessment was conducted at three month intervals throughout the 18 month study period. This included asking the patient about relief of their Rome III symptoms, and re-administration of the SF-8 to assess durability of relief of symptoms and

overall impact on QOL. Additional data for patients randomized to the surgical arm included operative and pathology findings and any associated operative complications.

Of note, patients in the non-operative management arm were allowed, at any time, to cross over to the surgical arm if they felt that their NO regimen was ineffective or they were unable to tolerate the amitriptyline. (CONSORT figure, Figure 1.)

Data analysis

All statistical analyses were performed by SAS 9.3 (SAS, Cary, NC). Statistical analyses were based on an intention-to-treat (ITT) principle. The chi-squared test was used for assessing differences in proportions. The student t-test was used to compare the means of both groups. In order to determine the normal distribution of the variables the Kolmogorov-Smirnov-test was used. Analysis of the SF-8 involved calculating the Physical Component Summary (PCS) and Mental Component Summary (MCS) for each patient. Comparisons of first visit, first follow-up visit, and last visit were performed using the Wilcoxon rank sum test. A two-tailed probability value of <0.05 was considered to be statistically significant.

Results

In all, thirty patients were enrolled over 12 months (15LC, 15NO). Of the 15 patients in the LC group, 13 underwent LC, one refused surgery, and one withdrew from the study. In the NO group, 14 crossed over to the LC group - of which 13 proceeded to LC - yielding a total of 26 patients who underwent LC and only one who elected to remain on amitriptyline. Of the 14 patients that crossed over, the median number of days until cross over was 3.5 (range 0–88). The one patient who elected to remain on medical (NO) therapy continues to well and is pain free at 15 months follow up.

For all patients, the median age was 43 years (range, 18–74) with 69.0% being women and 93.1% being white (Table 2). Of the 26 gallbladders removed, all showed evidence of chronic cholecystitis on final pathology, and none had associated stones or sludge. With median follow-up of 12 months [range 3–14], all 26 reported amelioration of symptoms, specifically relief of biliary pain as defined by the Rome III criteria. SF-8 physical scores (PCS-8) were significantly improved at both the first and last follow-up visits (Table 2). SF-8 mental scores (MCS-8) were also significantly improved at both the first and last follow-up visits (Table 3). When comparing the SF-8 scores by NO and LC groups (based off of intent-to-treat), no statistically significant results were found.

Discussion

This study, although a pilot project, represents the largest prospective experience to date examining the role of LC in the treatment of BD. In addition, the results are strengthened by the standardization of enrollment criteria and testing methodology. Consequently, these data are important for a number of reasons, but to fully appreciate their impact one must be familiar with the controversies and knowledge gaps surrounding the surgical treatment of BD.

Cholecystokinin-cholescintigraphy (CCK-HIDA) is commonly performed to evaluate patients with upper abdominal pain thought to be biliary in origin and with a gallbladder found to be normal on ultrasound. Cholecystectomy is commonly recommended in these patients based on the finding of an abnormally low gallbladder ejection fraction ¹. Although used commonly in today's clinical practice, the testing methodology and treatment outcomes pertaining to diagnoses related to the test – specifically biliary dyskinesia (or functional gallbladder disorder, as it is sometimes called) - are controversial and poorly understood by many practicing clinicians, as is the data (or lack thereof) supporting LC as the treatment of choice ^{2,5}. The following paragraphs detail the controversies surrounding the testing methodology, the method of determination of normal vs. abnormal CCK-HIDA values, and the data both supporting and questioning its clinical use to select patients for cholecystectomy based on the most current available literature.

For years, surgeons, gastroenterologists and primary care physicians have encountered patients in their practices that have presented with complaints consistent with biliary pathology, but with negative ultrasound imaging of the gallbladder, thus creating a diagnostic dilemma.

In 1991, a randomized, prospective study was published by Yap et al. in which a population of patients with suspected pain of biliary origin (and a negative gallbladder ultrasound) underwent CCK-HIDA scanning with calculation of the GBEF. Those with an abnormal GBEF, defined as <40% in their study, comprised the primary study group, and were randomized to either cholecystectomy or no cholecystectomy (observation) groups. Patients with a low GBEF who underwent cholecystectomy did dramatically better than those who were treated with observation. The remainder of the patients – those with pain but a with a normal ejection fraction - were treated at the discretion of the clinician (surgery vs. no surgery). Those that had a normal GBEF that underwent surgery did no better than those that were observed. The conclusion of the Yap study was that a low GBEF was predictive of success in patients who underwent cholecystectomy for acalculous biliary pain. Based on these data, clinicians began offering cholecystectomy to patients who met these criteria ⁶.

The Yap study, although interesting and widely quoted, has a number of criticisms that are worth noting. First, the size of the study population of patients with a low GBEF was only 21 patients - 11 surgery, 10 observation. Of the 11 undergoing surgery, 10 experienced total relief and one experienced improvement. Of the 10 in the observation group, all remained symptomatic, and two of these crossed over to the surgery arm and subsequently did well ⁶. Amazingly, this remains the only other randomized prospective trial to date examining the role of surgery in treating this condition, and was harshly criticized in a 2008 Cochrane review for not only being severely underpowered in terms of sample size, but also at significant risk of bias ⁷. In addition, the inclusion criteria were poorly described and no validated method for objectively assessing improvement was utilized.

Other data on the efficacy of CCK-HIDA in predicting response to cholecystectomy have been published with conflicting results, with success rates ranging from no correlation to a 96.6% cure rate ^{4,12}. A systematic review by DiBaise et al. examined this issue and found that the calculation of the GBEF was useful in selecting patients for surgery and predicting

successful treatment in 19 of 23 papers studied, including Yap et al.⁴ However, the investigators noted that the studies were small, nonrandomized, retrospective, uncontrolled, and with varying durations of follow up, varying symptoms used to define biliary pain, and varying definitions of successful outcomes. These flaws and the heterogeneity of the data make it difficult, if not impossible, to draw any evidence based conclusions from these studies.⁴ Once again, in these reviews and retrospective studies, randomized controlled trials were called for by the authors. Interestingly, the majority of the literature on this topic has been published from institutions in the United States, where it is estimated that 80% of all surgery for biliary dyskinesia in the world is performed.⁵

To understand the shortcomings of Yap et al. and other published studies, and the current knowledge gaps that exist in this area of clinical practice, one must also understand the controversies surrounding the performance of the CCK-HIDA scan itself. A key aspect of the CCK-HIDA scan is the manner in which normal vs. abnormal gallbladder ejection fraction results are determined, and how this differs from other diagnostic tests. With the majority of diagnostic tests, an abnormal value is *predictive of pathology* – for example, the finding of gallstones on ultrasound, a spiculated density on mammography, or an infiltrate on chest X-ray. CCK-HIDA is distinctly different however, in that the normal vs. abnormal values for GBEF are calculated from values obtained from *normal subjects*, with the cutoff of normal vs. abnormal typically designated at two standard deviations from the mean^{10,11,13}. In other words, the values are calculated from what is “normal” in the general population and “abnormal” values, by definition, are therefore not necessarily predictive of a disease state. They simply are values that fall outside the normal distribution obtained from performance of the test on healthy subjects. For this reason, it is expected that some normal volunteers will have an abnormal GBEF. Conversely, some patients with functional biliary pain may have GBEF values within the normal range.

Additionally, much controversy exists in the testing methodology. CCK-HIDA, despite widespread use in clinical practice, suffers from a lack of standardization of test methodology in a number of key areas. These include dose of CCK administered, duration of administration, and time at which GBEF is calculated. A review of the published studies on the use of CCK-HIDA revealed CCK doses from 0.005mcg/kg to 0.03 mcg/kg, infusion durations ranging from 2–3 minutes all the way up to 45 minutes, and normal vs. abnormal cutoff values ranging from 35%–65%. In some published studies, the exact nature of the testing protocol was not even described, including what values were considered to be abnormal¹⁴. This is relevant, since the technique of CCK-HIDA administration has been shown in prospective studies to affect the reproducibility of the results.¹³ For these reasons, in our study it was mandated that the CCK-HIDA scan be performed using the protocol endorsed by the Society of Nuclear Medicine as the most reliable and reproducible, which is a weight based (0.02mcg/kg) dose of CCK, infused over 60 minutes at which time the GBEF is calculated and the threshold for normal is set at 38%.^{10,11}

Patient selection may also be an issue that has affected the reliability of CCK-HIDA in predicting symptom relief after cholecystectomy. Current expert opinion based on the available data favors cholecystectomy for patients with biliary symptoms and an abnormal GBEF, and discourages cholecystectomy in cases involving atypical symptoms^{1,15}. The

definition of what constitutes the most appropriate and valid description of biliary symptoms is a matter of debate and has been a source of controversy in previous published reviews on this subject ⁴. Symptoms however remain crucial in selecting which patients should undergo diagnostic biliary testing, including CCK-HIDA. Furthermore, in the review by DiBaise and Oleynikov, the authors commented that a standardized and reliable set of diagnostic criteria for functional biliary pain was important in selecting patients for further biliary testing (CCK-HIDA) ⁴. The results of their pooled analysis revealed that outcomes were better in selected patients – ie. those with biliary symptoms and an abnormal GBEF, while outcomes were not improved in patients with biliary symptoms and a normal GBEF when compared with observational controls ⁴.

Other misconceptions involving patient selection for surgery based on the results of CCK-HIDA are worth mentioning. One such misconception is that the degree of lowering of GBEF is predictive of success. (In other words, a GBEF of 3% is more likely to have a favorable response to cholecystectomy than a patient with the same symptoms but a GBEF of say, 24%). This has not proven to be the case in the data published to date ¹⁶. Another misconception involves the idea that the reproduction of patient symptoms with CCK injection is another predictor of successful response to cholecystectomy. This assumption has proven to be false in published literature as well. CCK is known to stimulate other organs besides the gallbladder, including the small intestine and stomach, which may produce unpleasant pain and cramping. When administered intravenously, especially in a 2–3 minute infusion protocol, unpleasant symptoms are not uncommon and have no predictive value with respect to relief of biliary pain with cholecystectomy ^{2,17}.

These data, although once again limited by the retrospective nature of the studies examined, the heterogeneity of the pooled data, and the high risk of bias, suggest the need for reliable diagnostic criteria in the selection of patients for CCK-HIDA, since it is the combination of typical symptoms and an abnormal GBEF that appear to provide the best chance of success with operation. In our study, the symptom complex was standardized by the use of the Rome III criteria as the definition of biliary symptoms. These criteria were applied prospectively in the selection of patients, which once again, is crucial in assessing response to treatment and resolution of symptoms. The Rome III criteria for functional gallbladder disorder (Table 1) is perhaps the most well-known standardized symptom complex for the diagnosis of functional gallbladder disorder and the subsequent selection of patients to undergo CCK-HIDA scanning for suspected BD ⁹. The ordering of CCK-HIDA studies in patients with atypical symptoms not suggestive of functional biliary disorder should be discouraged, as some of these patients may indeed have an abnormal GBEF in the absence of disease ^{10,11}. Failure to grasp this concept may result in inappropriate referrals for surgery, thereby subjecting the patient to unnecessary risk and a higher likelihood of a failure to improve with cholecystectomy.

Our study, although a small pilot study, is currently the largest prospective experience to date examining the role of LC in treating BD, and provides the highest quality data to date supporting the role of LC in treating patients with BD. In addition, the above concerns raised in previously published literature were addressed in our study design. Specifically, only patients who met the Rome III definition of biliary dyskinesia were included. Patients with

other causes of abdominal pain or atypical symptom were excluded. The patients were administered a standard QOL assessment preoperatively (SF-8) and were then followed postoperatively with the same tool to allow a valid and objective measure of symptom relief and the durability of relief. Finally, only patients who had their CCK-HIDA scan administered in accordance with the current SNM recommendations were enrolled. Those who had studies that were not in compliance with the SNM guidelines were excluded or had their studies repeated properly.

There are several limitations to this study. First of all, because this was a pilot study the sample size is quite small, so the results will subsequently need to be reproduced on a larger scale before they can be fully embraced by the surgical community. Also, the choice of amitriptyline was based on its use in other functional gastrointestinal disorders and chronic pain syndromes. Although we feel that this was reasonable to do and preferable to a placebo for feasibility reasons – specifically, encouraging enrollment by providing an actual medical treatment rather than placebo- we acknowledge that there is no “gold standard” medical treatment for BD. In addition, the near 100 percent crossover rate from the medical to the surgical group precluded any effective evaluation of the effectiveness of the amitriptyline on patient symptoms. One could also question if a longer mandatory duration of medical treatment prior to crossover to the LC group would have resulted in a lower crossover rate, by giving the amitriptyline more “time to work.” The same could also be asked regarding titration of the amitriptyline to a higher dosage in non-responders. Although these are logical questions, in our initial exploratory studies we found it exceedingly difficult to enroll patients if a long trial of medical therapy was required, so early crossover was allowed for feasibility reasons relating to enrollment of subjects. Finally, the use of the SF-8 as our primary objective means of outcomes measurement could be criticized because it is not a disease-specific questionnaire. The SF-8 was chosen for its brevity and ease of administration, and although not specific to gastrointestinal disorders, does accurately assess improvement in both physical and mental well-being and overall QOL. It may be beneficial in subsequent studies to look at other QOL assessment measures to measure outcomes or to possibly develop a survey tool specific to BD. To do this is impossible however, until LC is definitively proved in larger studies to be an effective treatment for BD.

Ultimately we conclude, based these data, that LC is an effective treatment for BD, and that it provides durable and objective amelioration of symptoms as indicated by statistically significant improvement in a validated quality of life scoring system (SF-8). We also feel that, based on our observed high rate of crossover, that a similar larger randomized controlled trial may not be feasible, as the lack of a “gold standard” medical therapy and a strong bias toward surgery by both patients and referring clinicians made enrollment and adherence to a non-surgical treatment exceedingly difficult. Blinded “sham operation” trials examining LC vs. diagnostic laparoscopy, although attractive in concept, would be very costly, raise ethical concerns, and likely suffer from difficult enrollment or attrition as well. For these reasons, we feel that the role of LC in the treatment of BD may be best examined by a large, multi-center prospective cohort study, one again emphasizing strict symptom/ inclusion criteria, standardized methodology for the performance of the CCK-HIDA scan and determination of GBEF, standardized definitions of success measured objectively by a

validated survey tool, and an extended period of follow up. We look forward to continuing to contribute to the evolving body of knowledge on this very controversial topic.

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Figure 1.
CONSORT Figure – Study Design

Table 1**The Rome III Criteria for Functional Gallbladder and Sphincter of Oddi Disorders⁹**

I. Functional gallbladder and sphincter of Oddi disorders *:
1. Episodes lasting 30 minutes or longer
2. Recurrent symptoms occurring at different intervals
3. The pain builds up to a steady level.
4. The pain is severe enough to interrupt the patient's daily activities or lead to an emergency room visit
5. The pain is not relieved by bowel movements
6. The pain is not relieved by postural change
7. The pain is not relieved by antacids
8. Exclusion of other structural diseases that would explain the symptoms
Supportive criteria:
The pain may present with one or more of the following:
1. Associated with nausea and vomiting
2. Radiates to the back and/or right infrascapular area
3. Awakens patient from sleep in the middle of the night.
II. Functional gallbladder disorder (Must include all of the following)
1. Criteria for functional gallbladder and sphincter of Oddi disorder
2. Gallbladder is present
3. Normal liver enzymes, conjugated bilirubin, and amylase/lipase

* Must include episodes of pain located in the epigastrium and right upper quadrant and all of the following

Table 2

Baseline demographics

Characteristic	Total (n=29 [*])
Group, n (%)	
Surgical	14 (48)
Non-surgical	15 (52)
Gender, n (%)	
Male	9 (31)
Female	20 (69)
Race, n (%)	
Caucasian	27 (93)
African American	1 (3)
Other	1 (3)
Age, y, mean (median)	43.8 (43)
Gallbladder ejection fraction, %, mean $\pm$ SD	19.8 $\pm$ 11.7
Follow-up months, mean (median)	10.5 (12)

*
30 enrolled, 1 withdrew

Table 3

Comparison of Initial, First Follow-Up Visit, and Last Visit SF-8 Scores for All Patients Who Underwent Laparoscopic Cholecystectomy

	Initial	1st visit after surgery	p Value	Last visit	p Value*
General health (Q1)	41.2 ± 8.3	49.2 ± 7.3	0.0008	49.4 ± 7.4	0.0009
Physical functioning (Q2)	40.7 ± 9	47.4 ± 7.7	0.0027	48.7 ± 6.5	0.001
Role physical (Q3)	40.8 ± 9.7	48.6 ± 7.9	0.0001	49.7 ± 7.9	0.0002
Bodily pain (Q4)	40.7 ± 8.7	53.6 ± 8.6	<0.0001	52.2 ± 10.1	<0.0001
Vitality (Q5)	41.8 ± 8.1	50.5 ± 9.6	0.0013	50.4 ± 8.1	0.0009
Social functioning (Q6)	42.2 ± 9.7	49.5 ± 8.8	0.0015	51 ± 8.4	0.0001
Mental health (Q7)	44.5 ± 10.1	49.8 ± 9.2	0.1056	51.7 ± 7.6	0.001
Role emotional (Q8)	41.4 ± 8.3	48 ± 7.3	0.0014	48.5 ± 8.4	0.0035
Physical (PCS-8)	39.1 ± 9.3	50 ± 8.2	<0.0001	49.9 ± 8.8	0.0003
Mental (MCS-8)	44.4 ± 9.4	50.3 ± 9.5	0.0187	51.8 ± 9.6	0.0017

All values expressed as mean scores ± SD (standard deviation)

* p values refer to differences in scoring on the individual SF-8 components between the referenced visits

SF-8, "Short form-8" Health Survey; Q, Question; PCS, Physical component summary; MCS, Mental component summary