

Clinical Research Article

Patient and Provider Perspectives on Postsurgical Recovery of Cushing Syndrome

Rachel Acree,¹ Caitlin M. Miller,¹ Brent S. Abel,¹ Nicola M. Neary,² Karen Campbell,³ and Lynnette K. Nieman^{1,2}

¹Diabetes, Endocrinology and Obesity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA; ²Program on Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA; and ³Cushing's Support and Research Foundation, Plymouth, MA 02360, USA

ORCID numbers: 0000-0002-7512-357X (R. Acree); 0000-0003-1490-250X (C. M. Miller); 0000-0002-3598-0542 (B. S. Abel); 0000-0003-0534-8025 (L. K. Nieman).

Abbreviations: CD, Cushing disease; CRM, cortisol replacement medication; CS, Cushing syndrome; CSRf, Cushing's Support and Research Foundation; HRQOL, health-related quality of life; IQR, interquartile range.

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Abstract

Context: Cushing syndrome (CS) is associated with impaired health-related quality of life (HRQOL) even after surgical cure.

Objective: To characterize patient and provider perspectives on recovery from CS, drivers of decreased HRQOL during recovery, and ways to improve HRQOL.

Design: Cross-sectional observational survey.

Participants: Patients (n = 341) had undergone surgery for CS and were members of the Cushing's Support and Research Foundation. Physicians (n = 54) were Pituitary Society physician members and academicians who treated patients with CS.

Results: Compared with patients, physicians underestimated the time to complete recovery after surgery (12 months vs 18 months, $P = 0.0104$). Time to recovery did not differ by CS etiology, but patients with adrenal etiologies of CS reported a longer duration of cortisol replacement medication compared with patients with Cushing disease (12 months vs 6 months, $P = 0.0025$). Physicians overestimated the benefits of work (26.9% vs 65.3%, $P < 0.0001$), exercise (40.9% vs 77.6%, $P = 0.0001$), and activities (44.8% vs 75.5%, $P = 0.0016$) as useful coping mechanisms in the postsurgical period. Most patients considered family/friends (83.4%) and rest (74.7%) to be helpful. All physicians endorsed educating patients on recovery, but 32.4% (95% CI, 27.3-38.0) of patients denied receiving sufficient information. Some patients did not feel prepared for the postsurgical experience (32.9%; 95% CI, 27.6-38.6) and considered physicians not familiar enough with CS (16.1%; 95% CI, 12.2-20.8).

Conclusion: Poor communication between physicians and CS patients may contribute to dissatisfaction with the postsurgical experience. Increased information on recovery, including helpful coping mechanisms, and improved provider-physician communication may improve HRQOL during recovery.

Key Words: Cushing's syndrome, recovery, health-related quality of life

First-line treatment of Cushing syndrome (CS) is surgical resection of the primary disease-causing lesion, which may be a pituitary tumor in the case of Cushing disease (CD), an ectopic ACTH-secreting tumor, or ACTH-independent adrenal lesion(s) [1]. However, the sequelae of chronic hypercortisolemia, including cardiovascular, musculoskeletal, metabolic, cognitive, and psychiatric disease, may persist long after surgical cure [2–7]. Patients also require cortisol replacement medication (CRM) after surgery to avoid adrenal insufficiency and life-threatening adrenal crisis until the hypothalamic-pituitary-adrenal axis recovers [1, 8].

Health-related quality of life (HRQOL) is decreased in CS, and it remains lower than the reference population after biochemical remission is achieved [9–14]. A recent meta-analysis of 2643 patients with CS demonstrated that HRQOL and cognitive functioning improve but do not normalize to those of the general population after treatment [15]. An Endocrine Society Clinical Practice Guideline on CS treatment recommends lifelong management of the comorbidities associated with chronic hypercortisolemia to improve mortality and HRQOL [1].

Drivers of reduced HRQOL have been explored [16–19]. These include patient dissatisfaction with the medical profession regarding diagnosis, treatment, and aftercare for CS. Patients cite delays in diagnosis after the onset of symptoms [17, 18], a lack of adequate information and education about treatment and recovery [16, 17], and a dearth of health care professionals who are informed about CS [16, 18] as particularly detrimental to quality of life.

To design interventions aimed at improving HRQOL during remission from CS, a robust understanding of patients' perspectives on the postsurgical recovery process is needed. Given physicians' advisory role, and the dissatisfaction of patients with the quality of that relationship, it is also important to understand the physicians' perspectives on recovery. To our knowledge, no data exist on providers' opinions of or approaches to CS recovery.

Our survey approach was designed to further characterize patients' experience of recovery from CS, identify modifiable factors that may contribute to reduced HRQOL after surgical cure, and to compare patients' and physicians' perspectives on the recovery from this disease. Importantly, we attempted to incorporate both questions

with “objective,” quantifiable answers, and others that could be interpreted using a hermeneutic phenomenology approach.

Methods

This study had 2 phases. The first was an open-ended patient survey designed to identify themes in patients' responses regarding challenges during postsurgical recovery and helpful coping mechanisms. The second was broader in scope and targeted both patients and physicians; themes identified in the first phase were given as possible responses to questions about challenges and coping mechanisms, and open-ended questions also were included. Because no personally identifiable information was collected, the Intramural National Institutes of Health Office of Human Subjects Research Protections determined the study to be exempt from institution review board evaluation.

Phase 1 survey

In the first phase, patient members of the Cushing's Support and Research Foundation (CSRF) (approximately 400 members), were invited to complete an open-ended survey about their experiences after surgical treatment of CS in late 2008. The 7-question survey asked about the type of CRM, the duration of its use and tapering/testing strategies for its discontinuation, and the experience of recovery including both challenges and helpful coping mechanisms, as shown in Table 1.

Ninety-three responses were collected. Two respondents were excluded for answering only the first question, leaving 91 patients included in the analysis. All patients reported having resection of a specific lesion followed by initiation of CRM; this was considered confirmation of CS remission. For this report, 1 author (R.A.) reviewed all open-ended responses and clustered them into thematic groups.

Phase 2 surveys

In the second phase, we developed 2 web-based surveys based on responses of the phase 1 open-ended survey. One survey targeted patients in remission after surgical treatment of CS and was promoted through CSRF newsletter

Table 1. Phase 1 patient survey questions

1. What was the cause of your Cushing syndrome?
2. Are you currently taking cortisol (Cortef, hydrocortisone, prednisone, dexamethasone) replacement medication?
3. If you are no longer taking cortisol replacement medication, how long after your surgery were you able to discontinue replacement medication?
4. If you are no longer taking cortisol replacement medication, please describe the tapering procedure you used and what tests you had done before discontinuing replacement.
5. How would you describe the recovery process?
6. What did you find helpful in coping with the recovery process?
7. If you consider yourself recovered, how long did your recovery take?

and emails to approximately 915 patients from December 2010 to September 2011. Responses were collected from December 2010 to November 2011. This 27-question survey asked about the cause of CS; type and time of surgery; the type; dose and duration of CRM; decisions about discontinuation of CRM; postsurgical symptoms; whether and how patients received information about the experience during recovery; time to return to work; what helped during recovery; and length of recovery (Table 2). Answers were selected using a drop-down menu; additional open-ended responses could be added. A final open-ended question asked for any additional feedback and what might have improved the recovery experience.

A total of 385 patients submitted responses. Forty-four submissions were excluded from analysis: 2 were cases of exogenous CS, 2 patients had not yet had surgery, 1 was a duplicate, 1 was in the immediate postoperative period, 3 were taking ketoconazole, 1 was awaiting repeat surgery, 7 answered ≤ 3 questions, and 27 included only demographic information. As a result, 341 patients were included in the analysis, of which 332 reported having resection of a specific lesion followed by initiation of CRM. Of the 9 who did not indicate that they received postoperative cortisol replacement, 3 stated that cortisol levels were normal, 1 had adrenal insufficiency after surgery, 1 had undergone unilateral adrenalectomy, and 5 listed no medications or additional treatments. We considered these 341 patients to be in remission after surgery.

A second survey targeted endocrinologists. It was promoted through mailings to adult endocrinology fellowship training programs in the United States and the United Kingdom, and through an email announcement by the Pituitary Society. Responses were collected from December 2010 to November 2011. This 22-question survey asked about the type of practice and number of CS patients seen annually and to date; the type; dose and duration of CRM; decisions about discontinuation or taper of CRM based on minimal dose and testing; the type and delivery of information about the recovery period; the time to discontinuation of CRM and to full recovery;

patients' overall recovery experience; and what suggestions they make to improve that experience (Table 3).

Sixty-one endocrinologists responded to the physician survey. Seven responses included only demographic information and were excluded, leaving 54 responses included in the analysis.

Survey responses were obtained using an anonymized, secure, online platform (Clinical Trials DataBase, hosted by the National Institute of Child Health and Human Development), accessed via a link provided in the outreach notifications.

Statistical analysis

No respondent answered every survey question, so the total number of responses for each question varied in both the patient and physician surveys. In general, only questions with response rates $> 80\%$ were analyzed. Exceptions to this included if the question had a lower response rate because it was not applicable to every respondent or if it provided important contextual information. Such cases are noted. Open-ended responses were reviewed and clustered into thematic groups; when themes in open-ended responses directly answered closed-ended questions in the survey that were left blank by the respondent, responses were aggregated. When this methodology was used, it is noted when presenting the results.

Descriptive statistics included mean or median results with SD or interquartile range (IQR). One outlier response about time to recovery (158 months) was excluded because it seemed unlikely to be correct. The percentage of responses was calculated based only on questions that were answered; because not all respondents answered all questions, the number (n) of responses differed. Open-ended text answers were organized by themes and counted. Unpaired t tests, χ^2 analysis, Mann-Whitney U tests, Wilcoxon signed-rank tests, or 2-proportion z tests were used for comparisons where appropriate. P values and 95% CIs are reported. P values were adjusted using the Bonferroni correction in all χ^2 post hoc analyses.

Table 2. Phase 2 patient survey questions

1. What is your sex? *Male, female*
2. What is your age in years?
3. In what country do you live?
4. What was the cause of your Cushing syndrome? *Pituitary, adrenal, other, unknown, other*
5. Have you had surgery to treat your Cushing syndrome? *Yes, no*
6. How many surgeries have you had to treat your Cushing syndrome?
7. What was the date of your most recent surgery for treatment of your Cushing syndrome?
8. Check one option below that describes your surgery. *Pituitary, adrenal, other*
9. When you were discharged from the hospital after surgery, which cortisol replacement medication did you take? *Hydrocortisone, prednisone, dexamethasone, prednisolone, none, unknown, other*
10. What was the cortisol replacement medication dose that you were discharged on from the hospital after surgery?
11. Are you currently taking any type of cortisol replacement medication? *Yes, no*
12. If yes, what medication are you taking now? *Hydrocortisone, prednisone, dexamethasone, prednisolone, none, unknown, other*
13. What is the total daily dose?
14. If no, what medication was the last cortisol replacement medication you took after surgery? *Hydrocortisone, prednisone, dexamethasone, prednisolone, none, unknown, other*
15. How long after your surgery did you stop taking cortisol replacement medication? Please answer in months.
16. How did you take your cortisol replacement medication over time? *None, constant, decreased, unknown*
17. If you selected “decreased” for question 16, please select the option that best describe your tapering process. *Begin rapid, begin slow, end rapid, end slow, equal, unknown*
18. Who initiated the decision to stop or reduce your cortisol replacement medication? *Doctor, myself, both, unknown*
19. Which tests if any were performed after you were discharged from the hospital? *ACTH blood test, cortisol blood test, ACTH stimulation test, ITT, cortisol urine test, dexamethasone suppression test, no tests, unknown*
20. Except for sick days, did you ever increase your dose of cortisol replacement therapy? *Yes, no, unknown*
21. Were you ever changed to a different cortisol replacement medication? *Yes, no, unknown*
22. Have you taken any of the following medical therapies since your surgery? *Ketoconazole, metyrapone, mitotane, no medical therapies*
23. How would you describe your overall recovery experience? *Positive, negative, mixed, neutral*
24. After your surgery, did you lose weight? *Yes, no, unsure*
25. Are you now satisfied with your weight? *Yes, no, unsure*
26. After your surgery, did you suffer from lethargy (lack of energy)? *Yes, no, unsure*
27. After your surgery, did you suffer from pain in your joints? *Yes, no, unsure*
28. After your surgery, did you suffer from mental exhaustion? *Yes, no, unsure*
29. After your surgery, did you suffer from depression? *Yes, no, unsure*
30. Did you receive sufficient information about the postsurvey recovery experience? *Yes, no, unsure*
31. Who gave you information about the post-survey recovery experience? *Endocrinologist, neurosurgeon, both, neither, other*
32. Do you think those close to you were adequately prepared for your postoperative recovery? *Yes, no, unsure*
33. Would a standardized information sheet about the postsurgical experience from a professional organization of endocrinologists be helpful? *Yes, no, unsure*
34. Have you returned to work yet? *Yes, no, unemployed*
35. If yes to question 34, how many months after surgery did you return to work?
36. When you returned to work, did you work full time or part time? *Full time, part time, other*
37. What did you find helpful in coping with the recovery process? *Friends and family, physicians, support groups, physical therapy, exercise, analgesia, antidepressants, massage, entertainment, activities, work, rest, religion, none, other*
38. If you consider yourself recovered, how long did your recovery take? Please answer in months.
39. Was or is your recovery time longer than you expected? *Yes, no, unknown*
40. Do you have any other thoughts that you would like to tell us about your recovery experience after surgical treatment for Cushing syndrome? What could have improved your recovery experience?

For questions with associated drop-down menu options, those options are listed next to the question. All questions had an open-ended option. ITT, insulin tolerance test.

Results

Phase 1: open-ended patient survey

Ninety-one patients submitted a complete survey response, 78 (85.7%) of whom were female and 9 (9.9%) of whom were male; the remaining 4 respondents' sex identity was unknown. Most had CD (63/91; 69.2%), whereas 30.8% (28/91) had a

primary adrenal cause of CS. No patient indicated an ectopic source of ACTH as an etiology. No patient underwent bilateral adrenalectomy.

Of the 91 patients, 25 (27.5%) were taking CRM at the time of the survey. Subjects who had discontinued CRM estimated that they received treatment for a median of 10.5 months (IQR, 6-18; range, 0-108; n = 54).

Table 3. Phase 2 physician survey questions

1. How did you hear about this survey? *Email, letter, both*
2. What is your sex? *Male, female*
3. What is your age range? *20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+*
4. In what country do you live?
5. How would you describe your practice setting? *Hospital, office, other*
6. How many patients do you see with surgically-treated Cushing syndrome each year?
7. Approximately how many patients have you seen with surgically treated Cushing syndrome in total throughout your medical career?
8. What type(s) of cortisol replacement medication do you usually use after surgical treatment for Cushing's syndrome?
Hydrocortisone, prednisone, dexamethasone, prednisolone, other
9. If you use more than one type of cortisol replacement medication, how do you choose which medication to use?
10. What is the range of time that your Cushing patients take to discontinue cortisol replacement medication? What is the approximate median?
11. What recommendations do you tend to make to patients taking cortisol replacement medication after surgery for Cushing syndrome? *Nontaper, taper*
12. What is the lowest dose of hydrocortisone would you use for a Cushing patient before completely stopping therapy?
13. What is the lowest dose of prednisone would you use for a Cushing patient before completely stopping therapy?
14. What is the lowest dose of dexamethasone would you use for a Cushing patient before completely stopping therapy?
15. What is the lowest dose of prednisolone would you use for a Cushing patient before completely stopping therapy?
16. What is the lowest dose of other cortisol replacement medication would you use for a Cushing patient before completely stopping therapy?
17. Regarding routine (non-sick day) therapy, who initiates changes in cortisol replacement medication? *Myself, patient, both*
18. Which tests, if any, do you perform to assess whether patients should stop replacement therapy?
19. Except for sick days, have any of your patients increased their dose of cortisol replacement therapy? *Yes, no*
20. How would you describe your patients' overall recovery experience on average? *Positive, negative, mixed*
21. What information do you routinely provide to your patients regarding the recovery experience after their surgery? *Length of recovery, medication use, symptom recovery, nothing in particular, other*
22. Does the neurosurgeon operating on your patient routinely provide information to your patients regarding the recovery experience?
Yes, no, unknown
23. How do you give patients information regarding the recovery experience after their surgery? *Discussion, written, other*
24. Do you routinely include family and/or significant others in this education process? *Yes, no*
25. Would you welcome a standardized information sheet from a professional organization (such as the Endocrine Society or Pituitary Society) to help educate your patients and their relatives about their postsurgical recovery? *Yes, no, use my own*
26. Which of the following do you suggest to patients as helpful during the recovery process? *Friends and family, support groups, physical therapy, exercise, analgesia, antidepressants, massage, entertainment, activities, work, rest, religion, education, none, other*
27. What is the range of time you think it takes for your patients to fully recover after their surgery? What is the approximate median number?

For questions with associated drop-down menu options, those options are listed next to the question. All questions had an open-ended option.

Although all survey respondents self-reported being in surgical remission, not all patients considered themselves recovered. Forty-two respondents (46.2%) indicated they had not yet recovered at the time of the survey. Patients who did consider themselves recovered reported a median recovery time of 22 months (IQR, 12-27; range, 0-50; n = 48).

The most frequently cited challenge in recovery reported in an open-ended question was the long duration of recovery (37/91; 40.7%; 95% CI, 31.1-51.0), followed by pain (29/91; 31.9%; 95% CI, 23.2-42.0) and fatigue (22/91; 24.2%; 95% CI, 16.6-33.9). Fourteen patients reported neuropsychiatric impairment (15.4%; 95% CI, 9.4-24.2), an aggregate category that included responses about memory loss, inability to focus, depression, anxiety, and mood changes. Seven patients (7.7%; 95% CI, 3.8-15.0) reported nausea or loss of appetite during the recovery period.

Patients were asked what they found helpful in coping with the recovery process in an open-ended question (Table 4). The most helpful coping mechanisms described by respondents in the phase 1 survey were family and friends (38.5%), support groups (23.1%), rest (16.5%), and exercise (16.5%).

Phase 2: surveys of patients and endocrinologists

Respondent characteristics

Most patient respondents identified as female (312/341, 91.5%), 25 identified as male (7.3%), and 4 did not choose either option (male or female). Respondents reported a median age of 43 years (IQR, 33-53; range, 12-76; n = 337). The majority had CD (234/338, 69.2%), whereas 26.9% had a primary adrenal cause of CS (91/338) and 3.8% reported unknown or other etiologies (13/338). Patients with

Table 4. Useful coping mechanisms reported by patients and physicians

Coping mechanism	Phase 1 patient survey (N = 91)		Phase 2 patient survey (N = 337)		Phase 2 physician survey (N = 49)		P value ^a
	% (n)	95% CI	% (n)	95% CI	% (n)	95% CI	
Work	2.2 (2)	0.6-7.7	28.4 (96)	23.9-33.5	65.3 (32)	51.3-77.1	<0.0001
Religion	8.8 (8)	4.5-16.4	41.5 (140)	36.4-46.9	8.2 (4)	3.2-19.2	<0.0001
Exercise	16.5 (15)	10.2-25.4	42.7 (144)	37.6-48.1	77.6 (38)	64.1-87.0	<0.0001
Massage	3.3 (3)	1.1-9.3	23.1 (78)	19.0-27.9	2.0 (1)	0.4-10.7	0.0172
Family/friends	38.5 (35)	29.1-48.7	82.8 (279)	78.4-86.4	87.8 (43)	75.8-94.3	NS
Rest	16.5 (15)	10.2-25.4	73.9 (249)	69.0-78.3	42.9 (21)	30.0-56.7	0.0003
Physicians	15.4 (14)	9.4-24.2	49.0 (165)	43.7-54.3	-	-	-
Support groups	23.1 (21)	15.6-32.7	45.4 (153)	40.1-50.7	57.1 (28)	43.3-70.0	NS
Activities	6.6 (6)	3.1-13.6	44.8 (151)	39.6-50.2	75.5 (37)	61.9-85.4	0.0016
Entertainment	4.4 (4)	1.7-10.8	37.7 (127)	32.7-43.0	12.2 (6)	5.7-24.2	0.0117
Analgesia	8.8 (8)	4.5-16.4	30.3 (102)	25.6-35.4	18.4 (9)	10.0-31.4	NS
Antidepressants	3.3 (3)	1.1-9.3	30.3 (102)	25.6-35.4	36.7 (18)	24.7-50.7	NS
Physical therapy	2.2 (2)	0.6-7.7	13.9 (47)	10.7-18.1	28.6 (14)	17.9-42.4	NS
Other	44.0 (40)	34.2-54.2	11.6 (39)	8.6-15.4	4.1 (2)	1.1-13.7	NS
Nothing helpful	0.0 (0)	0.0-5.1	2.4 (8)	1.2-4.6	4.1 (2)	1.1-13.7	NS
Education	-	-	-	-	30.6 (15)	19.5-44.5	-

^aStatistical comparison between phase 2 survey patients and physicians is shown, and was obtained using 2 proportion z tests with subsequent Bonferroni correction. Abbreviation: NS, not significant.

CD underwent significantly more surgeries than patients with an adrenal cause of CS (mean, 1.5 vs 1.1; $P = 0.0258$).

The median time since last surgery for CS was 34 months (IQR, 17-74; range, 0.5-405; $n = 162$), though this information was only available for 47.5% of respondents. Whether the patient was in the upper or lower 50th percentile of time since last surgery did not affect their responses to questions about perception of recovery, coping mechanisms used during recovery, primary source of information on recovery, CRM management, or return to employment, nor were there differences in sex or CS etiology between the 2 groups.

Of the 54 physician responses, 15 were from women (27.8%). Most respondents were aged 40 to 49 (17/52, 32.7%) or 50 to 59 (18/52, 34.6%). Most were hospital-based (42/53, 79.3%), whereas a few worked either in a medical office (6/53, 11.3%) or an academic setting (4/53, 7.6%). Respondents practiced in the United States ($n = 10$), the United Kingdom ($n = 3$), Italy ($n = 3$), or elsewhere ($n = 10$) including Argentina, Australia, Brazil, Canada, Germany, Mexico, Netherlands, New Zealand, Portugal, and Spain (response rate, 48.1%). Over the course of their careers, endocrinologists reported seeing a median of 100 surgically treated CS patients (IQR, 42.5-200; range, 10-400; $n = 53$). There was no correlation between age of physician and number of surgically treated CS patients seen.

Type, duration, and management of cortisol replacement medication

Endocrinologists and patients reported a similar duration of CRM following surgery ($P = 0.95$), with physicians reporting a median of 9 months (IQR, 6-12 months; range, 3-15; $n = 48$) and patients reporting a median of 8 months (IQR, 5-14; range, 0-82; $n = 172$; response rate, 50.4%). Among patients, reported CRM duration differed by CS etiology. Patients with CD reported a median CRM duration of 6 months (IQR, 4-12; range, 0-40; $n = 113$), whereas patients with adrenal etiologies reported a median duration of 12 months (IQR, 6-18; range, 2-82; $n = 57$), a significantly longer timeframe ($P = 0.0025$).

Physicians' most commonly reported CRM was a hydrocortisone taper (35/54; 64.8%; 95% CI, 51.5-76.1), which they most frequently discontinued at a daily dose of 5 mg (11/35; 31.4%; 95% CI, 18.6-48.0) or 10 mg (13/35; 37.1%; 95% CI, 23.2-53.7). Prednisone (11/54; 20.4%; 95% CI, 11.8-32.9) and cortisone acetate (5/54; 9.3%; 95% CI, 4.0-19.9) also were reported. Less experienced endocrinologists, defined as those who had seen fewer than 100 patients with CS in their careers, were more likely to prescribe

hydrocortisone alone for recovery (21/26; 80.8%) than those who had seen 100 patients or more (13/27; 48.1%) by 32.6% (95% CI, 6.8-53.1; $P = 0.0133$). Neither physician age nor sex had an effect on likelihood of prescribing solely hydrocortisone.

The majority of patients reported that their physician decided when to stop or reduce their CRM (173/320; 54.1%; 95% CI, 48.6-59.4). However, 10.3% (33/320; 95% CI, 7.4-14.1) of patient respondents indicated they unilaterally made these decisions, and 35.3% (113/320; 95% CI, 30.3-40.7) said they worked in conjunction with their physician. There was no difference in these management decisions between male and female patients, and there was no relationship between management strategy and whether respondents described their recovery as positive, negative, or mixed.

Time to complete recovery

Endocrinologists reported a median time to complete recovery of 12 months (IQR, 9-18; range, 1-36; $n = 34$; response rate, 63.0%) following surgery. Patients who considered themselves recovered reported a median recovery time of 18 months (IQR, 12-24; range, 2-96; $n = 112$), a significantly longer duration than physicians described ($P = 0.0104$). Whether the patient was in the upper or lower 50th percentile of recovery time did not impact their responses to questions about perception of recovery, coping mechanisms used during recovery, primary source of information on recovery, CRM management, or return to employment, nor did reported recovery time differ by CS etiology or sex. Notably, among patients who considered themselves recovered and provided CRM duration, time to complete recovery was significantly longer than CRM duration (18 months vs 8 months, $P < 0.0001$, $n = 73$). This was also true for physicians who provided responses for both questions (12 vs 8 months, $P = 0.0001$, $n = 33$).

Patients returned to work a median of 3 months (IQR, 2-6; range, 0-120; $n = 132$; response rate, 38.7%) after their last surgical treatment. After surgery, 40.0% (113/284; 95% CI, 34.3-45.6) of patients went back to working full time, 38.0% (108/284; 95% CI, 32.6-43.8) worked part time, and 16.5% (47/284; 95% CI, 12.7-21.3) were unemployed; 5.6% (16/284; 95% CI, 3.5-9.0) described their return to work differently, such as working full time as a parent.

The experience of recovery

Most physicians and patients characterized the recovery experience as mixed (ie, having both positive and negative

elements; physicians: 16/27; 59.3%; 95% CI, 40.7-75.5 vs patients: 188/336; 56.0%; 95% CI, 50.6-61.2). A similar proportion of physicians and patients considered the experience to be primarily positive (physicians: 5/27; 18.5%; 95% CI, 8.2-36.7 vs patients: 90/336; 26.8%; 95% CI, 22.3-31.8) or negative (physicians: 6/27; 22.2%; 95% CI, 10.6-40.8 vs patients: 53/336; 15.8%; 95% CI, 12.3-20.1). The physician response rate to this question was 50.0%. Physicians' level of experience with CS patients had no association with their perception of patients' recovery. Among patients, the description of recovery was not associated with sex.

A total of 90.8% of patients responding to a question about whether they experienced "mental exhaustion during recovery" responded affirmatively (216/238; 95% CI, 86.4-93.8; response rate, 70.0%). A range of neuropsychiatric disturbances including memory loss, confusion, word-finding difficulties, difficulty concentrating, difficulties in social functioning, anxiety, and depression were reported in this answer. There was no statistical difference between the proportions of men and women endorsing mental exhaustion, nor between patients with CD and those with adrenal causes of CS.

Patients and physicians described different factors helpful to recovery (Table 4). Patient respondents reported family and friends (83.4%), rest (74.7%), physicians (48.4%), and support groups (44.5%) as the most helpful in their recovery. Physicians cited family and friends (87.8%), exercise (77.6%), activities (75.5%), and work (65.3%) as most helpful in patients' recovery. In contrast, a significantly smaller proportion of patients reported work (26.9% vs 65.3%, $P < 0.0001$), exercise (40.9% vs 77.6%, $P = 0.0001$), and activities (44.8% vs 75.5%, $P = 0.0016$) as helpful. Significantly fewer physicians reported religion (8.2% vs 42.9%, $P = 0.0002$), massage (2.0% vs 23.7%, $P = 0.0172$), and entertainment (12.2% vs 37.7%, $P = 0.0117$) as helpful coping mechanisms than did patients.

Information on recovery

Most patients reported receiving information about the recovery experience from a physician: either their endocrinologist alone (100/293; 34.1%; 95% CI, 28.9-39.7), their surgeon alone (22/293; 7.5%; 95% CI, 5.0-11.1), or both (76/293; 25.9%; 95% CI, 21.3-31.3). However, 32.4% of patients reported they did not receive information from either (95/293; 95% CI, 27.3-38.0). Many of these patients reported receiving information primarily from other sources, including through support groups and other patients (19/293; 6.5%; 95% CI 4.2-9.9) or their own online research (13/293; 4.4%; 95% CI, 2.6-7.5). There was no

statistical association between patients' reported experience of recovery (ie, positive, negative, or mixed) and where they received information on recovery.

All physician respondents reported giving information about the recovery process to patients in some way; 98.0% (49/50; 95% CI, 89.5-99.7) endorsed having a discussion about recovery and 38.0% (19/50; 95% CI, 25.9-51.9) endorsed giving written information. Sixty-two percent of respondents to this question indicated they rely solely on discussion, whereas 36.0% routinely use both discussion and written forms of information; 1 respondent endorsed using written information alone.

Endocrinologists also were asked whether the neurosurgeon operating on their patients routinely provides information about the recovery experience; of the 44 responses to this question, 14 (31.8%; 95% CI, 20.0-26.6) said yes, 21 (47.7%; 95% CI, 33.8-62.1) said no, and 9 (20.5%; 95% CI, 11.2-34.5) were unsure. Endocrinologists who did not believe or were unsure whether their neurosurgeons provided information on recovery were no more likely to offer multiple modalities of information (ie, both oral and written information) to patients than their counterparts who believed their neurosurgeon provided recovery information to patients. Few physicians (14.8%, 8/54) responded to a question asking whether they routinely include family members in their education process; of these, half said they did (4/8) and half said they did not (4/8).

Open-ended question on recovery

One question on the survey asked patients if they had any other thoughts about their recovery experiences and if there was anything that could have improved their experience. This was an open-ended question, but certain topics appeared frequently in responses (Table 5). Notably, 82.1% (280/341) of patients responded to this question; of these, 32.9% reported that they would have liked more information on what to expect going into their recovery or that they felt unprepared going into recovery, 16.1% felt as though not enough medical professionals were familiar with the symptoms of CS, 14.3% had difficulty with weight loss and/or suffered from persistent body image issues, and 12.1% reiterated the importance of support groups in their recovery.

Patients also described symptoms they experienced during recovery in this open-ended question (Table 5). A total of 18.6% complained of musculoskeletal pain, an aggregate category including any complaints of pain in joint, muscle, bone, back, knees, hips or body, and other comments such as "inability to stand for long periods," "shoulders froze and knees gave out," and "afraid the stress of standing would surely break my shins."

A total of 16.1% of respondents mentioned fatigue (statements referring to being tired, exhausted, weak, lack of energy/stamina, and lethargy) and 11.0% explicitly reported experiencing depression. Overall, 68.6% (234/341; 95% CI, 63.5-73.3) of patients surveyed reported experiencing at least 1 of musculoskeletal pain, fatigue, depression, or mental exhaustion in either a fixed-answer question or this open-ended question.

Additional selected quotations in response to this open-ended question that illustrate the anguish and pain felt during recovery are listed in Table 6.

Discussion

The postsurgical recovery from CS may be long and challenging. This large cross-sectional study brings to light underrecognized patient complaints about the experience of recovery while supporting existing data about long-term sequelae of chronic hypercortisolism.

Educating patients about recovery

The problem of insufficient information from medical professionals about postsurgical recovery has been reported previously in small studies [16, 17]. Our data support these findings; in our larger survey, one-third of patient respondents felt unprepared for recovery after surgery and wanted more information, whereas 16% reported that they felt that doctors gave them inaccurate information or were not knowledgeable about CS. Just over 10% named other patients, support groups, or their own online research as the primary source of information.

Although 100% of endocrinologist respondents provided oral or written information on recovery, 32% of patients denied receiving any information from a physician. This discrepancy may be influenced by the method of information sharing. Most physicians (62%) discussed recovery during patient visits; only 36% also used written materials. Use of multiple modalities and frequent review may be necessary, given the cognitive difficulties associated with CS. Written information about the patient's concerns/expectations or the multiplicity of potential experiences or might allow patients to feel understood, while providing a future reference.

The duration of recovery

Although 88% of physicians reported that they counseled patients about symptoms of remission, only 16.7% (8/48) reported advising that patients might feel worse before feeling better, or that recovery would be long. Several quotations illustrate the frustration of patients who were not told their

Table 5. Patient concerns mentioned in the final open-ended question of the phase 2 patient survey

Patient concern (N = 280)	% (n)	95% CI	Sample quotations
Felt unprepared for recovery and/or wanted more information on recovery	32.9 (92)	27.6–38.6	<p>“[I needed] better aftercare.”</p> <p>“I wish someone would have told me . . . what I would be experiencing after surgery.”</p> <p>“Information on how to recognize adrenal insufficiency/crisis would have been helpful.”</p> <p>“I am ‘in the dark’ as to what’s going on . . . at this point.”</p> <p>“Recovery from having Cushing’s has been really rough for me and my family. We had no idea what to expect, or how long it would take.”</p> <p>“A list of more critical symptoms in which we should call the doctor would have been great to avoid all of the nagging unsure phone calls in which we have to hear, ‘oh don’t worry, that’s normal.’”</p>
Providers were not familiar enough with CS or provided inaccurate information	16.1 (45)	12.2–20.8	<p>“I needed one single doctor who knew Cushing’s but could also act like a primary care [provider] while my body resolved multiple problems. My Cushing’s doctor wasn’t interested in helping me through the little stuff, and my primary care [provider] didn’t know anything about Cushing’s recovery.”</p> <p>“I am shocked that most medical professionals are NOT FAMILIAR with Cushing’s syndrome or its recovery.”</p> <p>“I just wish physicians were more familiar with Cushing’s. It is so frustrating . . . [and] adds to the mental exhaustion of trying to fight off this debilitating disease.”</p>
Difficulty with weight loss/persistent body image issues	14.3 (40)	10.7–18.9	<p>“I wish my endocrinologist had prepared me for what to expect in recovery . . . She said I would be able to return to work 2-3 weeks after surgery. It took me 3 months before I could return to work.”</p> <p>“I’m upset that I’ve put weight on and wish I could have liposuction . . .”</p> <p>“I lost some weight after the surgery, but never ever came close to coming near what I weighed before the surgery.”</p> <p>“The weight gain makes me feel horrible about how I look. My husband left after the surgery as he said he could not take the weight gain.”</p> <p>“I had a big problem with my body image after I lost weight after recovering. I still don’t feel very comfortable with my body.”</p>
Found/believed they would have found a support group beneficial to their recovery	12.1 (34)	8.8–16.5	<p>“Peer support regarding the range of recovery experiences . . . was something that I should have sought out earlier.”</p> <p>“I would have greatly benefited from a Cushing’s support group.”</p> <p>“Talking/reading up on people with the actual syndrome and how they handled [recovery] would have helped me out a lot more than going into the recovery process ‘blind.’”</p> <p>“I would encourage endocrinologists [to provide patients] with information on local or virtual support groups that deal with Cushing’s recovery.”</p>
Recovery was longer than expected	7.5 (21)	5.0–11.2	<p>“I started a blog and a support group for patients in the early diagnosis and recovery of Cushing’s. This allowed me to connect with others who were going through the same things I was and saved my sanity, knowing that I wasn’t alone.”</p> <p>“I think knowing how long the process could take . . . would have better prepared me.”</p> <p>“I thought I would undergo surgery and walk out of the hospital well. Two years later I’m still not completely back.”</p> <p>“A more realistic time frame for recovery [would have helped] . . . I expected a quick recovery.”</p> <p>“It really needs to be stressed to patients that it will take a really long time to get better.”</p>
Wanted more information on recovery for family members/felt misunderstood by family	3.9 (11)	2.2–6.9	<p>“Family members and patients need a more thorough education about the disease and symptoms as many of us spent years thinking it was our fault and something was wrong.”</p> <p>“Formal information about recovery from the doctor to patient and his/her family member probably [would] help a lot.”</p> <p>“I was not warned of all the physical things I would be going through (for example, joint pain, depression, physical exhaustion) so my family just thought I was crazy.”</p>

Table 5. Continued

Patient concern (N = 280)	% (n)	95% CI	Sample quotations
Experienced musculoskeletal pain	18.6 (52)	14.5–23.5	<p>“I had so much joint and muscle pain I could hardly move.”</p> <p>“I am very sore all of the time.”</p> <p>“My shoulders froze, my knees gave out.”</p> <p>“I never, never imagined I would go through such excruciating pain in the joints and muscles!”</p> <p>“The worst part of recovery is the physical fatigue.”</p> <p>“Not having energy to do things I expected to be able to do was very disappointing.”</p> <p>“[One of the] hardest parts of recovery for me was the lack of energy.”</p> <p>“I am still very tired.”</p>
Experienced fatigue	16.1 (45)	12.2–20.8	<p>“I felt ill-prepared for the severe depression I experienced.”</p>
Experienced depression	11.1 (31)	7.9–15.3	<p>“I did go to talk therapy on my own, but that should have been required by the endocrine team [as I had] many issues with depressive thoughts.”</p> <p>“I think an antidepressant should have been prescribed upon diagnosis of Cushing’s and sustained through recovery. My depression was debilitating, but avoidable.”</p>

Abbreviation: CS, Cushing syndrome.

recovery might span years (Table 5). Compared with endocrinologists, patients reported a significantly longer median duration of recovery (18 vs 12 months) and suggested a longer time to recovery after CRM cessation (8 vs 6 months, $P = 0.05$).

Time to recovery of adrenal function, defined as the time from successful surgery to cessation of CRM, differs according to CS etiology [20]. Our findings support that patients with adrenal etiologies of CS require CRM for longer than patients with CD. Notably, patients’ reported time to recovery did not differ by CS etiology in our study, suggesting that adrenal function does not affect patients’ perception of recovery. Patients who considered themselves recovered described a recovery time that significantly exceeded their duration of CRM, indicating this is a poor proxy for recovery.

Sex and recovery

The impact of sex on the recovery experience is unclear. Although some studies found that women report greater impairment in some components of HRQOL [10, 12, 21], others found no influence of sex [11, 18, 22]. Our results showed no statistical difference in perception of recovery between men and women, nor in prevalence of fatigue, depression, joint pain, or mental exhaustion. As with most studies of CS, our study included more women than men.

Coping mechanisms during recovery

The majority of patients and physicians cited family and friends as a helpful coping mechanism during recovery. Familial involvement in chronic disease management promotes self-management of disease as well as cohesion among family members [23, 24]. Including family in discussions on recovery also aids patients in later recall of information. Physicians can better harness the power of social support by sharing information on recovery with family members early in the recovery process. A small but striking subset of patients highlighted challenges in familial relationships: “my family just thought I was just crazy,” “[my family] think I’m just lazy,” and “recovery was very detrimental to my family and marriage.”

Physicians differed from patients in their opinions on useful coping mechanisms during recovery. Although there was agreement that supportive friends and family were helpful in recovery, significantly more physicians than patients cited work, exercise, and activities as helpful, and rest as less helpful, suggesting physicians may overestimate patients’ physical abilities during recovery. By contrast, significantly more patients than physicians cited religion,

Table 6. Patient quotations from an open-ended question about their experience of recovery

“I seriously thought about asking my doctors to put me in a medically induced coma, as sometimes is done with burn victims. I still wonder if that may be the best route for some CS patients after surgery.”

“If it had been left to the medical profession, I know I would have committed suicide by now. They removed my gland and sent me on my merry way.”

“There is a constant fear of recurrence that isn’t addressed.”

“I thought I was quite prepared for the physical problems associated with the recovery, [but] I was not expecting the mental torture! I had no idea that I would be suicidal at times . . . No one seemed to mention it. These things were much worse than when I actually had the disease!”

“I feel like my recovery would have been much easier if there had been more awareness of this disease. Friends were not there for me during my illness as they thought I ‘looked healthy’ and I really think some of them thought I was just crazy. (I even wondered that myself at times.)”

“Because Cushing’s is an invisible illness, many people think that because I’m smiling, or because I have a good day, or that because the tumor is gone, I’m healed . . . and that’s not the case at all. Once the tumor is gone, THEN everything starts to get bad.”

“I was told I was ‘cured’ of Cushing’s, however . . . I am sicker without the tumor than I was with it . . . If given the choice again, I would have left the tumor even if the result would have been death.”

“This is a scary and confusing disease. The recovery is long and tiresome, some days feeling like you will never be normal again. It would have been good to have known beforehand that it was going to be like this.”

“Cushing’s recovery was a horror. If I hadn’t had support groups on the Internet to know what to expect I never would have made it.”

“Recovery was more difficult than living with Cushing’s . . . Having Cushing’s makes you feel isolated and antisocial. Your body changes and your mind changes and sometimes those symptoms, along with the pain, are invisible to others.”

“Doctors that treat CS have never had CS and therefore cannot understand it in the way that CS patients understand it.”

“The whole experience from being diagnosed to recovery was very detrimental to my family and marriage. If more information had been made available to me, my recovery would have been viewed differently by my family and husband.”

“My family member still does not believe that I’m having a difficult time . . . They think that I’m just lazy.”

Abbreviation: CS, Cushing syndrome.

entertainment, and massage as helpful in recovery. Patients’ desire for spiritual care is frequently overlooked by providers or is confined to end-of-life care [25]. Our finding underscores this and suggests CS patients may benefit from questions from their provider to regarding their desire for religious or spiritual engagement throughout recovery.

Physicians also must consider the benefits of adjunctive nonmedical components of mainstream medicine; in addition to massage, patients espoused warm baths, hot tubs, Epsom salt soaks, acupuncture, and meditation. Encouraging patients to trial adjunctive tools during initial education may reduce frustration during recovery. Additionally, referral to a physical therapist acknowledges and addresses the reality of physical limitations. Physicians also may remind patients to engage in pastimes they enjoy, while recognizing that more physically and cognitively demanding activities may not be best for everyone right away.

Furthermore, as part of a multidisciplinary approach to recovery, patients may benefit from referral to a mental health professional. The lasting cognitive and psychiatric effects resulting from chronic hypercortisolemia are well-established [6, 14, 26, 27]. In our study, 11% of patients endorsed postoperative depression, although this is likely to be an underestimate because these responses were collected from an open-ended question on the experience of

recovery. Regardless, mental health professionals may support patients in the absence of overt psychiatric disease. For example, others have suggested that reduced self-esteem may contribute to discouragement and decreased engagement in the recovery process [14, 28]. Difficulty with weight loss, endorsed by 14% of patients in our study, is 1 possible driver of reduced self-esteem. One patient offered, “The weight gain makes me feel horrible about how I look.” Another remarked, “I had a big problem with my body image after I lost weight after recovering. I still don’t feel very comfortable with my body.” Therapy can offer patients tools to cope with these challenges

Our findings lend credence to prior research showing improved HRQOL and/or self-efficacy in patients with diabetes mellitus [29–31], chronic kidney disease [32], chronic heart failure [33], and cancer [34, 35] who participated in educational programs. This fits well with the phenomenologic characterization of patient goals to understand their illness and create a cognitive framework of what may be expected [36]. Patient-centric educational programs typically involve education on disease pathogenesis, diet and physical exercise, stress reduction methods, medication management, and recognizing disease-specific emergencies. In particular, the self-management tools do not fit a medical paradigm that lumps patients into a diagnostic category with variable prognosis, but rather focus

on individual experiences and ways to alleviate those problems. Given the protracted nature of CS recovery and survey respondents' desire for information about recovery, similar interventions may be beneficial in CS. Disease-specific support groups, endorsed by nearly half of patient respondents, also can assist because many offer written materials [37–39] and provide forums on recovery where concerns can be addressed from the patient's perspective.

The unexpected utility of open-ended questions in understanding recovery

Many respondents did not answer questions with drop-down (fixed) answer choices but gave them in a final open-ended question asking about additional thoughts. For example, less than 3% of survey respondents answered a fixed-answer question about joint pain during recovery, but 19% of respondents included comments about musculoskeletal pain in the open-ended question. Possible explanations for this discrepancy include cognitive difficulties leading to lack of focus or inability to synthesize experiences into a conclusion.

It is also possible that patients do not relate to the experience of “joint pain,” but will endorse “pain in back and feet,” or “feeling as though my legs might break.” Few patients answered a closed-ended question that asked about “lethargy (lack of energy),” but 45 included, for example, “lethargic,” “tired,” “fatigue,” or “lack of energy” in an open-ended question. An open-ended question about mental exhaustion also elicited a variety of responses: “have to reread in order to grasp the context,” “forget simple words,” “moving underwater feeling,” or “couldn't make the easiest decisions, for example between a blue or red shirt.”

The implications of the differences in closed and open-ended responses are important. The diversity of responses we observed underscores the danger of relying on closed-ended questions when interviewing patients about their symptoms. Patients, particularly those experiencing cognitive difficulty, might have trouble identifying their subjective experience of what the medical community calls “lethargy” or “memory problems,” thereby causing a provider to misjudge recovery progress or even overlook the diagnosis of CS. Understanding that patients do not conceptualize their experience of illness into a neat list of symptoms is critical to improving patient-physician communication. Furthermore, many patients might not notice gradual changes and will not report them even if asked open-ended questions. The astute physician will elicit critical information by providing examples more recognizable to patients; instead of asking, “Are you experiencing memory problems?” a question such as, “Are you having

more difficulty remembering your grocery list?” might be more salient.

Limitations of the study

We characterized nearly all patients as being in surgical remission based on their use of CRM; the survey methodology did not provide a more definitive way to ascertain if this was correct. However, reduction in HRQOL in CS despite biochemical remission is well established and our findings are in line with these previous reports [2, 4, 5, 7, 9–14, 21, 22, 28, 40, 41]. Furthermore, the validity of responses unrelated to CRM are not contingent upon biochemical data supporting remission because they describe the experience of the overall recovery period.

Additionally, our data were collected in the past decade, raising the question of whether the postsurgical experience has improved. Recent studies suggest patients continue to report unmet needs regarding postsurgical care, including a lack of information about what to expect during recovery and a desire for more support from health care professionals, employers, family, and support groups [16, 17]. We believe that this continued discontent reflects a lack of physician consideration of the patient experience, and further suggests the importance of a patient-centric phenomenologic approach to recovery. Regardless, an update on whether patient-provider relationships have evolved is certainly of interest.

Further limitations of this study include the recall bias inevitable when asking patients to recount their experience of illness, as well as low response rates to some questions. Also, recruitment through the CSRF may have influenced our findings because patients who actively participate in support groups may not be representative of all CS patients. Despite this, raising physician awareness of the negative aspects of recovery for some patients remains important. Finally, our findings may not be generalizable to patients with ectopic ACTH-secreting tumors, who may experience the added complexity of possible oncologic disease.

Opportunities to improve the experience of recovery from CS

Our study, the first to compare patient and provider perspectives of the CS recovery experience, revealed divergent understanding of recovery between patients and physicians. The gaps between patients' perception of the adequacy of information on recovery, the high number of physicians asserting that they provided information, and different perceptions of the time to full recovery all suggest different understandings of the word “recovery.” When approached from the epistemology of science and medicine,

“recovery” may mean normalization of biochemical data, whereas when understood from the patients’ narrative of the experience of recovery [42], many additional factors may be summed in the concept of “recovery.” It has been noted that physicians approach disease from the perspectives of diagnosis, treatment, and prognosis, which is a Boolean prognosticator that does not actually predict the future for the patient. By contrast, patients seek explanation, cure, and prediction of their course [36]. When physicians fail to understand a patient’s conception of recovery and provide information that only meets their own definition, it is not surprising that the patient feels resentful and physicians feel inappropriately categorized.

Overall, our findings reveal patients’ desire for more information from physicians on postsurgical recovery, including its duration, what symptoms to expect, and helpful coping mechanisms. We suggest use of written materials, as well as reinforcement of the concepts related to recovery at each visit, to improve patient education. Physicians might use the information from these surveys and their own patient’s response to open-ended questioning to create a more diverse toolkit to cope with the challenges of recovery. Additionally, explicit education of partners and family may increase social support and help others to accept the difficulties encountered during recovery. We hope that our findings will lead to greater physician understanding of recovery from this disease and foster deeper discussion and understanding between physicians, patients, and their families.

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Additional Information

Correspondence: Lynnette K. Nieman, MD, Bldg 10-CRC Rm 1-3140, 10 Center Drive, Bethesda, MD 20892, USA. Email: niemanl@mail.nih.gov.

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