Luna AI-VR Study
Scientific Analysis and Report

Prepared by Lilach Gavish, PhD

Protocol title:

Pilot Study of Luna, an Artificial Intelligence-Virtual Reality (AI-VR) Intervention for Improving Symptoms Associated with Hot Flashes in Female Cancer Patients

Study dates:

First Recruitment to completion date: 26-February-2018 to 1-Oct 2018

Study officials/Investigators:

- Muhammad Rashid Abbasi, M.D., Principal Investigator

Study Sponsor:

- RHealth Ltd

Accompanying documents:

- Study Tables
- Study Figure

Executive Summary

Hot flashes and night sweats (HF/NS) are frequent side effect of endocrine therapy or chemotherapy for breast cancer patients associated with social embarrassment, discomfort, and distress. Moreover, HF/NS events may interfere with cancer therapies, and existing pharmacological therapies have undesirable side effects.

The Luna AI-VR is a virtual reality (VR) coaching environment that offers a psychological intervention to reduce the intensity and frequency of HF/NS.

A clinical study evaluating the efficacy of the Luna AI-VR intervention in breast cancer patients suffering from hot flashes was conducted. The clinical trial began in 26-February-2018 and completed in 1-Oct. A total of 37 female subjects with breast cancer and experiencing hot flashes as side effects of the treatments completed the protocol. The women used the intervention daily for 24 days. Study evaluations were conducted before and after the intervention.

This report contains an analysis of the demographic, clinical, physiological, and patient reported outcome data collected in the Luna AI-VR study.

Following Luna AI-VR intervention, breast cancer patients reported 50% less hot flash/ night sweat events, reduced average intensity, reduced levels of psychological distress related to health concerns, and decreased levels of interference in their daily activities. The most positively affected aspects were work and sleep and were characterized by less sleep disturbances, decreased daytime dysfunction, and improved sleep quality.

No adverse events related to the device were reported in the database, and physiological measures were not affected by the intervention.

It should be noted that this study was non-controlled and non-blinded and therefore the validity of the results is limited. Nevertheless, the results of this pilot study are a major step towards finding a safe and efficient non-pharmacological approach for reduction of this debilitating side effect of breast cancer patients and survivors and promoting their physical and psychological well-being.

Contents

Abbreviations

BIPQ	Brief Illness Perception Questionnaire
DCIS	Ductal Carcinoma In Situ
HF	Hot Flash (or Flush)
HFPRS	HF problem rating score
HFRDIS	Hot Flash Related Daily Interference Scale
HRS	Hot flash Rating Scale
IDC	Invasive Ductal Carcinoma
K10	Kessler Psychological Distress Scale
NS	Night Sweats
PSQI	Pittsburg Sleep Quality Index
PSS	Perceived Stress Scale
SD	Standard Deviation
WHOQOL	World Health Organization Quality of Life Questionnaire

Background and Rational

Breast cancer patients and survivors frequently experience acute menopausal symptoms such as hot flashes and night sweats that can be described as sudden increased skin temperature, skin conductance (sweating) and heart rate and can last from 2-30 minutes per event [1]. These side effects are a manifestation of changes in hormonal levels that effect the body thermoregulation and are a result of chemotherapy, ovarian suppression, or endocrine therapy (anti-estrogens, etc.) [2]. Both hot flashes and night sweats interfere with daily life: while hot flashes are associated with social embarrassment, discomfort, and distress, night sweats are associated with sleep problems and fatigue. These side effects may also affect compliance with the anticancer therapies[3]. For these reasons, it is important to find an effective intervention to reduce their occurrence. Available pharmacological treatments directed to alleviate vasomotor symptoms include clonidine, gabapentin, selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. However, the adverse effects of these treatments are also undesirable [4, 5]. Cognitive behavioral therapies were shown to be effective in reducing intensity and frequency of hot flashes [6].

The Luna AI-VR is a virtual reality (VR) coaching environment in a winter wonderland setting called Frosty that offers a psychological intervention based upon cognitive behavioral therapy (CBT) and mindfulness- based stress reduction (MBSR) protocols.

The current study was designed to determine the efficacy of the Luna AI-VR intervention in breast cancer patients suffering from hot flashes. For a detailed overview of background material, eligibility criterions, study procedures, and relevant approvals, see the study protocol.

This report contains an analysis of the data collected in the Luna AI-VR study.

Methods

Data source

Data of the study was retrieved from 2 sources:

Paper CRFs (“Patient signed documents”) that were filled by the study coordinator containing demographic and clinical data (based on the patient medical files) as well as physiological data that was measured at the baseline and follow up visit. These CRFs were scanned and the data was retrieved and typed into an electronic database.

Study Brochures (“HF_Pre_Pilot_survey” and “HF_Post_Pilot_survey”) that were filled by the patients at baseline and follow up containing demographic and clinical data, as well as questionnaires. The data from these brochures was located in 2 finalized digital databases.

Data completeness

Demographic and clinical data based on the medical files presided over data collected from the patients when there was a discrepancy. One patient did not arrive at the follow up and her physiological measurements are not available. However, the patient completed the “HF_Post_Pilot_survey” online. Missing survey values in follow-ups were completed by “Last observation carried forward”.

Surveys

The study surveys administered before and after the intervention period contained questions to assess subjective feelings of intensity, physical symptoms, psychological symptoms, and time to return to normal routine as well as questions that were taken from validated questionnaires pertaining to perceived stress, psychological distress, illness perception, sleep quality and quality of life. These questionnaires and their scoring method and interpretation will be detailed below. It should be noted that each questionnaire has a specific scoring system and several interpretations. The intent of this report was to choose the most appropriate interpretation for the specific patient population. Most of the questionnaires were validated for a specific period of time that is not always the specified period of time in this study.

Hot Flash Characteristics

The patient was required to score the average hot flash intensity from 1 (low) to 10 (very high). This was followed by a multiple-choice question pertaining to the physical symptoms accompanying HF events, including Shortness of breath, Rapid heartbeat, Internal heat, Sweat, Nausea, Dizziness, Headache, Weakness. Another question pertained to the psychological feeling following a HF. The patient was asked to mark one or more options including feeling agitated, frustrated, tired, or anxious. Finally, the patient was asked to evaluate the time to return to normal routine.

The Hot flash Rating Scale (HRS) – Q41-Q60

The HRS by Hunter and Liao [7] is used to evaluate the frequency of the hot flashes (HFs) and night sweats (NSs), as well as problem ratings (of distress, interference and perception of flushes as problematic). There are 2 measures based on these questions: Hot flush frequency total score = the total number of hot flushes and night sweats in the past week; Problem rating score = average scores of answers to extent of distress, interference, and perception of flushes as problematic

The Hot Flash Related Daily Interference Scale (HFRDIS)

The HFRDS by Carpenter [8] captures the extent in which the hot flashes interfere with different aspects of life. Each aspect is scored using an 11-point scale (0=does not interfere, to 10=completely interferes). The 10 scores are then averaged and divided according to cut points of mild (0 to 3.9), moderate (4 to 6.9) and severe (7 to 10)[9]. A minimal important difference (MID) is defined as an average change of 1.66 [9].

The Kessler psychological distress scale (K10)

The K10 [10], was used to assess the changes in the level of psychological distress. The K10 is comprised of 10 questions that are answered using a five-point scale (where 5 = all of the time, and 1 = none of the time). Scores are summed to a maximum score of 50 indicating severe distress, and the minimum score of 10 indicating no distress. The original interpretation by Kessler was used to assess the likelihood of having a mental disorder. However, for the patient population of the current study, the interpretation by Andrew and Slade [11] relating to the level of psychological distress is more appropriate.

K10 score	Level of psychological distress
10 - 15	Low
16 - 21	Moderate
22 - 29	High
30 - 50	Very High

An improvement score representing change between levels of the K10 based on before/after data was calculated (Worse=+1; No change=0; Improved=-1; Much improved=-2; Very much improved=-3).

The Perceived Stress Scale (PSS) by Sheldon Cohen

The Perceived Stress Scale (PSS) developed by Sheldon Cohen [12] measures the perception of stress by asking the patient to score the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. The questions in the PSS ask about feelings and thoughts during the last month. However, in this study the questions relate to the past 2 weeks. PSS scores are obtained by reversing responses (e.g., 0 = 4, 1 = 3, 2 = 2, 3 = 1 & 4 = 0) to the four positively stated items (items 4, 5, 7, & 8) and then summing across all scale items. Individual scores on the PSS can range from 0 to 40 with higher scores indicating higher perceived stress. The following interpretation is used regarding the level of perceived stress resulting from health concern [13].

PSS score	Level of Perceived Stress
0-7	Very Low
8-11	Low
12-15	Average
16-20	High health concern
21+	Very high health concern

The Brief-Illness Perception Questionnaire (BIPQ)

The BIPQ, developed by Broadbent [14], is a nine-item scale designed to rapidly assess the cognitive and emotional representations of illness. The items are rated on a scale from 0 (minimum) to 10 (maximum). The first five assess cognitive perceptions such as effect on life (item 1); duration of illness (item 2); control over illness (item 3); beliefs about the effectiveness of treatment (item 4); and experience of symptoms (item 5). Items 6 and 8 assess emotional aspects to include concern about illness and a multifaceted question about mood. Item 7 assesses degree of understanding of the illness. The final item is open-ended, asking respondents to rank the three most important factors causing their illness.

The Pittsburg Sleep Quality Index (PSQI)

The PSQI was used to assess sleep disturbance [15]. It contains 19 items that together produce a global sleep quality score and seven specific component scores (quality, latency, duration, disturbance, habitual sleep efficiency, use of sleeping medications, and daytime dysfunction). Global scores range from 0–21 with higher scores indicating poor sleep quality and high sleep disturbance. Global PSQI score of 5 or above was considered cutoff for sleep disturbances. Comment - Note a problem with the question numbers.

Luna AI-VR Study
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List of Tables:

Table 1: Demographic Characteristics

Age [years]		48.4 ± 6.4 [33-60]
Weight [Kg]		79.5±20.2
BMI [Kg/cm^2]		
	Normal	11 (30%)
	Overweight	8 (21%)
	Obese	18 (49%)
Country of birth		31 of 37 from the USA
Marital Status (%) [children, mean±SD]		
	Married/partnered	28 (76%) [1.6±0.9]
	Single	4 (11%) [0.5±1]
	Divorced/separated	5 (13%) [1.2±1.3]
Ethnicity		
	White	31 (84%)
	Hispanic	3 (8%)
	Asian	3 (8%)
Education		
	High school or less	7 (19%)
	College	10 (27%)
	Graduate or above	20 (54%)
Occupational Status		
	Employed full time	19 (51%)
	Employed part time	11 (30%)
	Not employed	7 (19%)
Household Income		
	<$50,000	6 (16%)
	$50,000-$99,999	7 (19%)
	$100,000-$149,999	7 (19%)
	≥$150,000	16 (43%)
	Chose not to answer	1 (3%)
Physical Activity		
	Yes	24 (65%)
	Sometimes	10 (27%)
	No	3 (8%)

Table 2: Clinical Diagnosis and Treatments

Diagnosis	
Breast Cancer	37* (100%)
Months since diagnosis	21±10 [4-41]
Years since diagnosis	1.8±0.8 [0.3-3.4]
History of breast cancer in the family	16 (43%)
Known mutation (BRCA / other)**	4 (11%)
Menopausal Status (at time of diagnosis)	
Premenopausal	30 (81%)
Postmenopausal	6 (16%)
Perimenopausal (transitioning menopause)	1 (3%)
Breast Cancer Stage	
Stage I	14 (38%)
Stage II	18 (49%)
Stage III	5 (13%)
Breast cancer type	
Ductal carcinoma in situ (DCIS)	11 (30%)
Invasive Ductal Carcinoma (IDC)	24 (65%)
Invasive Lobular Carcinoma	2 (5%)
Treatments	
Chemotherapy	22 (59%)
Surgery (lumpectomy/mastectomy)	32 (86%)
Radiotherapy	17 (45%)
Hormonal Therapy	
Tamoxifen	24 (65%)
Aromatase inhibitor	8 (22%)
Tamoxifen+AI	2 (5%)
Other	1 (3%)
Currently undergoing chemotherapy	3 (8%)

Data presented as counts (percent) or mean±SD [range]
*One case of primary breast cancer and secondary ovarian cancer
** 11 never tested

Table 3: Physiological Parameters Before and After Luna

Physiological Parameter	**Before**	**After**	**p-value***
Weight [Kg]	79.5±20.2**	78.4±20.9	0.045
Pulse [minute^{-1}]	78±13	76±11	0.179
Temperature [˚C]	36.9±0.3	36.9±0.3	1.00
Systolic Blood Pressure [mmHg]	128±16	128±17	0.894
Diastolic Blood Pressure [mmHg]	80±10	78±10	0.082
Respiratory Rate [minute^{-1}]	20.2±4.4	20.0±3.7	0.781

*by 2-tailed paired ttest; **mean±SD

Table 4: Hot Flush Symptoms

Hot Flush Characteristics	Before	After	p
HF average intensity	7 [2.5]	5 [4]	**<0.0001***
HF Symptoms			
Shortness of breath	6 (16%)	3 (8%)	
Rapid heartbeat	14 (38%)	12 (32%)	
Internal heat	29 (78%)	34 (92%)	
Sweat	34 (92%)	28 (76%)	
Nausea	2 (5%)	1 (3%)	
Dizziness	3 (8%)	4 (11%)	
Headache	4 (11%)	3 (8%)	
Weakness	1 (3%)	3 (8%)	
Feeling after a hot flash			
Agitated	11 (30%)	8 (22%)	
Frustrated	15 (41%)	20 (54%)	
Tired	11 (30%)	9 (24%)	
Anxious	8 (22%)	9 (24%)	
Other	3 (8%)	8 (22%)	
Time after hot flash to return to normal routine			
Immediately	27 (73%)	34 (92%)	
15-30 minutes	9 (24%)	0 (0%)	
1 hour or more	1 (3%)	3 (8%)	

HF average intensity was scored from 1 (low) to 10 (very high) and presented as median [IQR]. Before/after comparison was conducted *by Exact Wilcoxon Sign Rank test . HF symptoms, feeling after a hot flash, time categories to return to normal (1 or more) are reported as counts (percentages).

Table 5: Hot Flash Rating Scale: HF frequency total score and HF problem rating score

Measures of HFs/NSs	Before	After	p
HF frequency total score	49 [7-255]	22 [3-105]	**<0.0001***
Weekly #hot flushes	38.5 [3-193]	17.5 [3-88]	**<0.0001***
Weekly #night sweats	17.5 [0-70]	7 [0-49]	**0.001***
HF problem rating score	**6.8±1.9**	**4.8±2.2**	**<0.0001****
Perception as a problem	7.0 [3.0]	6.0 [3.0]	**<0.0001***
Distress	7.0 [3.0]	5.0 [3.3]	**<0.0001***
Interference	6.0 [3.3]	4.0 [4.0]	**<0.0001***

HF frequency total score and its' components are reported as median [range: minimum - maximum]. HF problem rating score is reported as mean±SD (normal distribution determined by Shapiro-Wilk), while the components are reported as median [IQR] (non-parametric data). Before/after comparison was conducted *by Exact Wilcoxon Sign Rank test **by paired ttest. $p \leq 0.05$ considered significant. Bonferroni's correction for multiple comparisons was used separately for components of each score - $p \leq 0.025$ for HF frequency components; $p \leq 0.017$ for HF problem rating components

Table 6: Hot Flash Related Daily Interference Scale (HFRDIS)

Hot Flash Interference		Before	After	p
Average Hot Flash Related Daily Interference Scale Score*		5.4±2.5	4.0±2.4	**<0.0001** Δ=1.5 [95%CI: 0.7,2.3] 21 of 37 reached MID
	Mild	11 (30%)	17 (46%)	
	Moderate	13 (35%)	15 (40%)	
	Severe	13 (35%)	5 (14%)	
Individual HRDIS Item Responses (range 0=do not interfere to 10=completely interfere				
1	Work (outside the home and housework)	6.0 [5.3]	3.0 [4.3]	**<0.0001**
2	Social activities	6.0 [5.0]	4.0 [4.3]	**0.003**
3	Leisure activities	6.0 [5.0]	4.0 [4.3]	**<0.0001**
4	Sleep	8.0 [4.0]	5.0 [5.3]	**<0.0001**
5	Mood	5.0 [4.0]	5.0 [4.3]	0.038 NS
6	Concentration	5.0 [4.0]	4.0 [4.5]	0.011 NS
7	Relations with others	4.0 [6.0]	3.0 [5.0]	0.034 NS
8	Sexuality	6.0 [7.5]	5.0 [7.0]	0.053 NS
9	Enjoyment of life	5.0 [5.0]	3.0 [6.0]	**0.005**
10	Overall quality of life	6.0 [4.3]	4.0 [5.3]	**<0.0001**

HFDRIS average score is reported as mean±SD (normal distribution determined by Shapiro-Wilk). Cut points of mild (0-3.9), moderate (4-6.9), severe (7-10) as well as the minimal important difference (Δ≥1.66) were determined according to Carpenter et al [4]. Before/after comparison was conducted by paired ttest. p≤0.05 considered significant. HFRDIS components are reported as median [IQR] (non-parametric data). Before/after comparison was conducted by Exact Wilcoxon Sign Rank test with Bonferroni's correction for multiple comparisons. p≤0.005 considered significant.

Table 7: Brief Illness Perception Questionnaire – Global Score and Components

Brief Illness Perception		Before	After	p
Global score BIPQ		40.3±15.1	36.8±14.6	0.092* NS
	Consequences	5.0 [5.0]	3.0 [4.3]	**0.004****
	Timeline	4.0 [6.0]	3.0 [5.3]	0.062 NS
	Personal control	5.0 [5.0]	6.0 [4.3]	0.813 NS
	Treatment control	3.0 [3.0]	3.0 [3.0]	0.388 NS
	Identity	6.0 [6.0]	5.0 [4.3]	0.912 NS
	Concern	8.0 [5.0]	6.0 [5.3]	**0.002**
	Understanding	3.0 [3.0]	3.0 [3.0]	1.000
	Emotional response	7.0 [4.0]	6.0 [3.5]	**0.003**

Global BIPW score is reported as mean±SD (normal distribution determined by Shapiro-Wilk), while the components are reported as median [IQR] (non-parametric data). Before/after comparison of global score was conducted * by paired ttest and for each component **by Exact Wilcoxon Sign Rank test with Bonferroni's correction for 8 multiple comparisons (p≤0.05 and p≤0.00625 considered significant respectively). Significant results were emphasized in bold.

Table 8: Pittsburgh Sleep Quality Index Global Score and Components

Pittsburgh Sleep Quality Index	Before	After	p
PSQI Global Score	9.6±4.4	7.3±4.1	**<0.0001**
PSQI>5: #patients (%)	33 (89%)	24 (65%)	
Subjective sleep quality	1.8±0.9	1.4±0.8	**0.003**
Sleep latency	1.1±0.8	0.8±0.8	0.035 NS
Sleep duration	1.2±1.0	1.0±1.0	0.016 NS
Habitual sleep efficiency	1.2±1.2	1.0±1.2	0.083 NS
Sleep disturbances	2.0±0.5	1.6±0.5	**<0.0001**
Use of sleep medication	1.0±1.4	0.8±1.2	0.282 NS
Daytime dysfunction	1.3±1.0	0.8±0.9	**<0.0001**

PSQI Global score and its' components is reported as mean±SD (in accordance with scientific literature). Global PSQI score ≥5 was considered cutoff for sleep disturbances. Before/after comparison of global score was conducted *by paired ttest. Bonferroni's correction for 7 multiple comparisons was applied to components. p≤0.05 and p≤0.007 for global and components respectively considered significant. Significant results were emphasized in bold.

Table 9: WHOQOL-BREF score

Quality of life scores	Before	After	p
Q1: How would you rate your quality of life?			
Very poor	0	0	
Poor	2 (5%)	2 (5%)	
Neither poor nor good	6 (16%)	2 (5%)	0.48 NS
Good	13 (35%)	18 (49%)	
Very good	16 (44%)	15 (41%)	
Q2: How satisfied are you with your health?			
Very dissatisfied	2 (5%)	1 (3%)	
Dissatisfied	8 (22%)	7 (19%)	
Neither satisfied nor dissatisfied	8 (22%)	6 (16%)	0.049 NS
Satisfied	17 (46%)	17 (46%)	
Very satisfied	2 (5%)	6 (16%)	
QOL Domains			
Physical	65±21	71±18	0.011 NS
Psychological	58±17	61±17	0.107 NS
Social relationship	70±24	69±24	0.456 NS
Environmental	77±15	77±16	0.898 NS

WHOQOL-BREF Q1 and Q2 presented as counts and percentages. QOL domains, raw data transformed to 100 scores and presented as mean±SD. Before/after comparison was conducted *by Wilcoxon Signs Rank test and by paired ttest for separate questions and domains respectively. Bonferroni's correction for multiple comparisons was applied to separate questions and domains (6 comparisons). p≤0.0083 was considered significant.

Luna AI-VR Study
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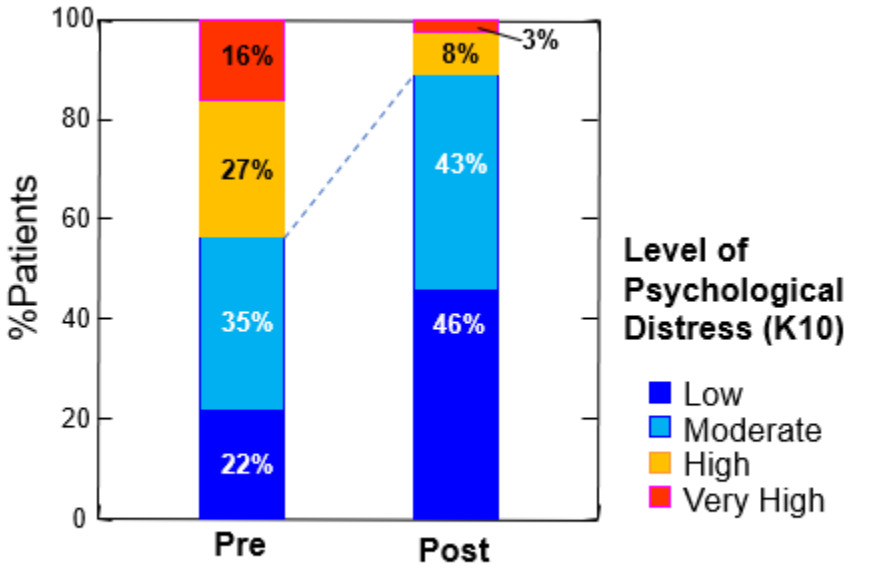
List of Figures:

Figure 1: Level of Psychological Distress based on K10 score – Before and After Luna

Patients were stratified according to level of distress using the Andrew and Slade interpretation of the Kessler score (K10). Stratified bar graph shows the percentage of patients by levels before and after Luna. Levels are color-coded.



Level of Psychological Distress by Andrew and Slade

Figure 2: Level of Psychological Distress – Improvement from Baseline

Change in level of psychological distress according to the interpretation by Andrew and Slade from before to after Luna. The arrows show the change from pre to post Luna (base to head of arrow respectively). The width of the arrow represents the number of patients, with the number itself written near the top of the arrow. Circles represent patients that did not report a change in level pre/post the study. The levels are color coded similar to the previous figure.

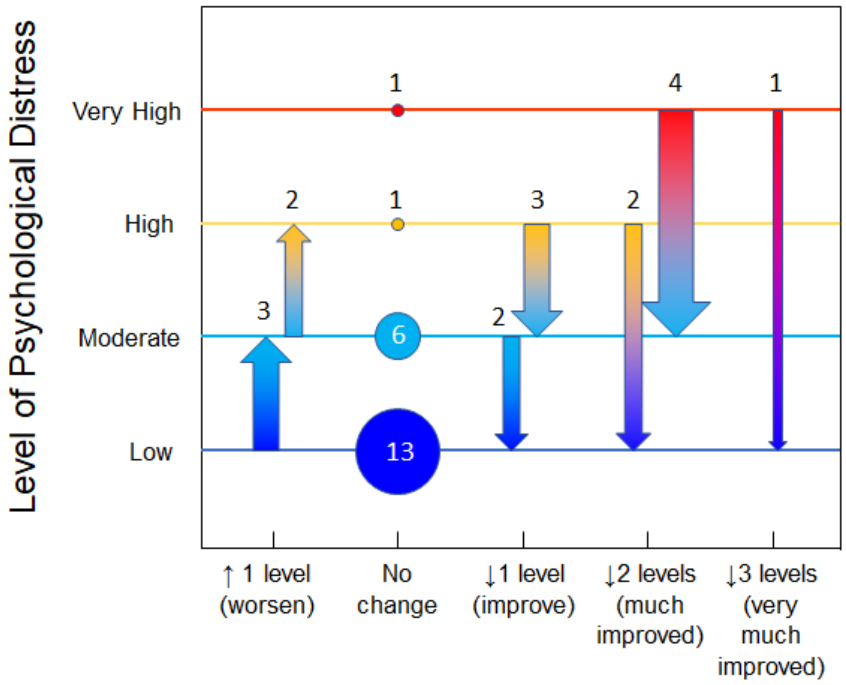


Figure 3: Level of Perceived Stress (PSS) Resulting from Health Concerns – Before and After Luna

Patients were stratified according to level of perceived stress scale. Stratified bar graph shows the percentage of patients by levels before and after Luna. Levels are color-coded.

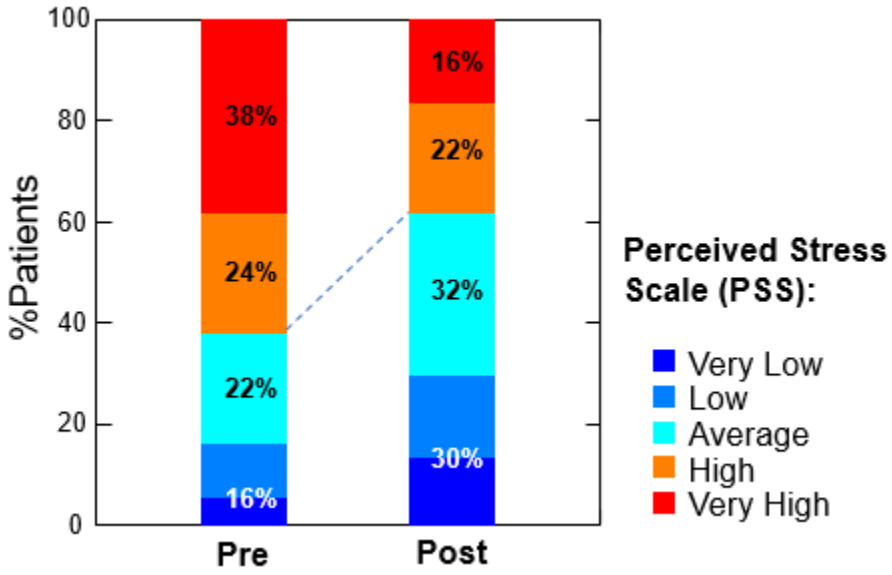


Figure 4: Pittsburgh Sleep Quality Index Components – Before and After using Luna

Bars represent mean±SEM for pre (full pattern) and post (striped pattern) intervention. *significant; **highly significant by paired ttest with Bonferroni's correction for multiple comparisons. PSQI components are color-coded.