


Dynamic Effects of CAM Techniques on Inflammation and Emotional States: An Integrative Single-Case Study on a Breast Cancer Survivor

Integrative Cancer Therapies
Volume 20: 1–11
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1534735420977697
journals.sagepub.com/home/ict


Christian Schubert, MD, PhD¹ , Michaela Ott, MA², Julian Hannemann, MA², Magdalena Singer, PhD³, Harald R. Bliem, PhD², Kurt Fritzsche, MD⁴, Christina Burbaum, PhD⁴, Emil Chamson, PhD⁵, and Dietmar Fuchs, PhD⁶

Abstract

Background: This study on a breast cancer survivor investigated how episodic practice of various complementary and alternative medicine (CAM) techniques affected the dynamics of emotional states and urinary neopterin—an inflammation marker. **Methods:** The 49-year-old female patient (diagnosis: ductal breast carcinoma 5 years before study start, suffering from chronic fatigue and depression) collected her entire urine in 12-hour intervals (from about 8 a.m. to 8 p.m. and from about 8 p.m. to 8 a.m.) for 28 days. The resulting 55 consecutive urine samples were analyzed for neopterin and creatinine levels using HPLC. Also in 12-hour intervals, the patient filled out questionnaires on emotional states and everyday routine, including CAM practice. Weekly, she was interviewed to identify emotionally meaningful everyday incidents, including use of CAM techniques. Time series analysis consisted of ARIMA modeling and cross-correlational analyses. **Results:** Qualitative evaluation revealed that, with the exception of Tai Chi, all CAM techniques, that is, Jin Shin Jyutsu, music, physiotherapy and energy healing, were experienced as positive. Cross-correlational analyses showed that practice of such CAM techniques was followed first by significant ($P < .05$) increases in positive mood and mental activity on the same day (lag 0) and then by decreases in positive mood after a total of 72 to 84 hours (+lag 6) and in mental activity after a total of 84 to 96 hours (+lag 7). Negative mood, by contrast, first decreased on the day of CAM practice (lag 0) and then increased after a total of 84 to 96 hours (+lag 7) following CAM. Moreover, urinary neopterin levels first increased on the day of CAM practice (lag 0) and then decreased after a total of 36 to 48 hours (+lag 3). Similar biphasic effects were also detected for irritation in response to CAM, although only partly significant. **Conclusion:** Cyclic psychophysiological response patterns following CAM practice were attributable to biopsychosocial feedback mechanisms involving personally meaningful experiences. As lower neopterin levels following CAM point to a health-promoting effect, the patient of this study may have actively contributed to her healing process through episodic CAM practice.

Keywords

psychoneuroimmunology, breast cancer, stress, inflammation, CAM

Submitted November 6, 2019; revised October 19, 2020; accepted November 4, 2020

Psychoneuroimmunology (PNI) is a modern research area in psychosomatic medicine that can be seen as the empirical realization of the biopsychosocial paradigm.¹ PNI deals with the complex interactions between psychosocial variables and parameters of the nervous, endocrine, and immune systems.² Studies in PNI have shown that chronic stress is connected to persistent activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis, leading to chronic elevations in stress hormone levels (catecholamines, cortisol [hypercortisolism]).³ Such

hyperactivity of the stress system makes it easier for cancer cells to proliferate, stimulates metastasis, and promotes chemotherapy resistance.⁴⁻⁷ Moreover, natural killer (NK) cell number and activity, which protects against cancer development, is reduced during prolonged stress.^{6,8}

In addition to immune suppression, chronic stress can affect malignant cell growth via inflammation due to insufficient counterregulatory activity of cortisol.^{9,10} Specifically, it has been shown that traumatic stress (eg, associated with cancer diagnosis and therapy¹¹) can be related to HPA axis



hypofunction, which is characterized by chronically reduced cortisol release (hypocortisolism) and/or glucocorticoid resistance in which glucocorticoid receptors in immune cells respond less sensitively to cortisol.^{9,12} Chronic inflammation not only lowers life expectancy in cancer¹³ but may also be responsible for a number of non-specific symptoms cancer patients often suffer from.¹⁴ This syndrome, called “sickness behavior,”^{15,16} includes neurovegetative symptoms such as cancer-related fatigue (CaRF), loss of appetite and sleep disorders as well as neuropsychiatric symptoms such as sadness/depression, loss of interest, and cognitive problems.

According to PNI, such complex psycho-immunological and immuno-psychological interactions must always be taken into account when serious diseases such as cancer are dealt with therapeutically.¹⁷ This is why complementary and alternative medicine (CAM) is becoming increasingly relevant for cancer patients.¹⁸ CAM interventions in cancer comprise a great number of techniques (eg, mind-body therapies, physiotherapy, biofield therapies, music) that consider not only physical aspects of a disease but also psychological, social and spiritual factors as well as their interactions.¹⁹

Considering the increasing interest in CAM techniques on the part of cancer patients and survivors, relatively few studies on their efficacy have been available to date, and even less is known about their mechanisms of action.²⁰ Although meta-analyses and reviews point to some favorable immune effects of CAM practice in breast cancer (eg, enhancing protective immune activity, lowering inflammation), findings become inconsistent when specific immune variables, such as circulating immune markers (eg, C-reactive protein [CRP], interleukin-6 [IL-6]) and measures of stimulated cytokine production, are taken into account.^{21,22} This inconsistency may be due to the lack of suitable research designs to investigate the complex biopsychosocial functions of CAM.²³ Conventional biomedical research methodology (eg, pre-post design, standardized methods, randomized controlled trial [RCT]) must be regarded as inadequate for evaluating the functional characteristics of CAM because it cannot grasp highly complex life phenomena, such as dynamic complexity and personal meaning, that are immanent components of such therapies.^{23,24}

The “integrative single-case study” design was developed by our research group in order to capture these complex biopsychosocial phenomena under conditions of “life as it is lived.”^{25,26} Specifically, within a period of 1 to 2 months, the subject collects his or her entire urine in 12-hour intervals,

fills out questionnaires every morning and evening, and is interviewed weekly to determine the past week’s emotionally meaningful everyday incidents. Through this procedure, a variety of psychosocial, psychological, and biochemical time series can be constructed. These can then be tested for temporal relationships via time series analysis.²⁷

In a recent integrative single-case study on a 49-year-old female patient with prior breast cancer and current CaRF and depression, the dynamic relationship between urinary neopterin concentrations, fatigue, and mood was investigated.²⁸ Neopterin, a marker of T helper cell type 1 (TH1)-mediated immune activity, is released by macrophages after interferon gamma (IFN γ) stimulation.²⁹ Its increase is a reliable indicator of inflammation and inflammation-related depression in breast cancer patients.³⁰⁻³² In that study, it was shown that increases in positive mood co-occurred with neopterin level increases and preceded decreases in neopterin concentrations with a temporal delay of 132 to 144 hours. Moreover, increases in urinary neopterin levels preceded increases in fatigue intensity with a temporal delay of 60 to 72 hours.²⁸

The present investigation re-evaluated the above-mentioned study on the same breast cancer survivor. This time, we focused on the influence of various CAM techniques on the patient’s urinary neopterin concentrations. As she suffered from depression and CaRF, we also examined potential connections between CAM and her emotional states (mood, irritation, mental activity). In accordance with the “life as it is lived” character of the integrative single-case study design, CAM practice was not planned in advance but was a natural part of the patient’s everyday life. In other words, the study was not an interventional study in which the participant was encouraged to apply a specific predefined intervention.

Methods

Study Design

This integrative single-case study belongs to a larger project on breast cancer survivors that investigates the influence of emotionally meaningful incidents on stress system functioning and CaRF. Various results from this study have already been published.^{28,33,34} Before study start, medical and psychological examinations were conducted to ensure that the patient, who had previously suffered from breast

¹Clinic for Medical Psychology, Medical University Innsbruck, Innsbruck, Austria

²Institute of Psychology, University of Innsbruck, Innsbruck, Austria

³Department of Medical Psychology, Center for Public Health, Medical University of Vienna, Vienna, Austria

⁴Department of Psychosomatic Medicine and Psychotherapy, Medical Center, University of Freiburg, Freiburg, Baden-Württemberg, Germany

⁵Department of Translation Studies, University of Innsbruck, Innsbruck, Austria

⁶Section for Biological Chemistry, Biocenter of the Medical University Innsbruck, Innsbruck, Austria

Corresponding Author:

Professor Christian Schubert MD, PhD, Department of Psychiatry and Psychotherapy, Clinic for Medical Psychology, Medical University Innsbruck, Schöpfstraße 23a, Innsbruck, A-6020, Austria.

Email: christian.schubert@i-med.ac.at

cancer, met the inclusion and exclusion criteria specified by Bower and colleagues in their investigation of breast cancer survivors with CaRF.³⁵ The only difference to the Bower et al. criteria³⁵ was that the patient of the current study had been diagnosed with dysthymia (F34.1) and adjustment disorder (F43.21).

For the purpose of the study, the patient collected her entire urine over a period of 28 days (from July 13th to August 9th, 2006) in 12-hour intervals (from approx. 8:00 p.m. to approx. 8:00 a.m. and from approx. 8:00 a.m. to approx. 8:00 p.m.), which led to a total of 55 equidistant measurements. Furthermore, she filled out various questionnaires on psychological variables (eg, emotional state, daily activity and routine, physical well-being) at approx. 8:00 a.m. and at approx. 8:00 p.m. Once a week, the patient brought the frozen (-20°C) urine samples to the laboratory, where they were stored at -70°C until analysis. At these regular weekly appointments in the clinic, the general health status of the patient was monitored, and she was interviewed regarding psychosocial incidents of the previous week.

The patient gave written informed consent for the study and for publication of the results, and the Ethics Review Committee of Freiburg University approved the design (application number: 137/07).

Patient Description

The patient is a 49-year-old woman. She has a university degree, is married and has 3 children. She is a non-smoker and consumes moderate amounts of alcoholic beverages. Five years before the study began, the patient was diagnosed with ductal breast cancer (C50.4) in the right breast (pT2, pN1biv (6 of 13), cM0, G3, R0, ER 10%, PR 70-80%, HER2+/neu+, score=3). The 5-year survival rate of this stage IIB breast cancer at the time of diagnosis was about 85%.³⁶ Therapy consisted of surgery, radiotherapy and anti-estrogen therapy with tamoxifen. Adjuvant therapy with tamoxifen ended 6 months before the start of the study. Both before and since her cancer diagnosis, the patient has suffered from dysthymia (F34.1).

Shortly after the cancer diagnosis and subsequent therapy, the patient developed severe CaRF and a substantial increase in depression intensity with clear functional impairment (clinical diagnosis: adjustment disorder with depressed mood, F43.21), both lasting until study start. The chronic depressive symptoms are probably due to the underlying dysthymia and adaptation problems triggered by regular follow-up cancer checks. The patient had undergone psychotherapy for 6 months, which ended 5 months prior to the start of the study.

At the beginning of the study, the patient was clinically free of evidence of metastatic or recurrent lesions. However, she showed the highest possible scores (20) on the "general fatigue" subscale of the Multidimensional Fatigue Inventory-20 (MFI-20), indicating CaRF. On the Center for Epidemiologic Studies Depression Scale (CES-D), the

patient scored 50 out of 60 possible points, indicating depression. In addition, on both the Spielberg STAI-S (State Trait Anxiety Inventory State) and the STAI-T (State-Trait Anxiety Inventory Trait), she had high anxiety values (78 and 69, respectively). The patient took aspirin on an irregular basis.

Determination of CAM Interventions

Daily Inventory of Activity, Routine and Illness (DIARI). The "Daily Inventory of Activity, Routine and Illness" (DIARI) was developed for daily follow-up studies such as the integrative single-case study.²⁵ The DIARI was completed every 12 hours and entailed answering questions about emotional states, everyday activity and routine (eg, physical activity, consumption of nicotine, alcohol and caffeine, sleeping habits, medication use) and illness-related issues (eg, possible infection, physical complaints, disturbing thoughts regarding cancer, level of fatigue, coping with cancer, social support). In addition, using the DIARI, the patient took notes on negative (stressful) and positive (relieving) everyday incidents every 12 hours. The DIARI requires approx. 10 minutes to fill out. In the current study, the patient's documentation of everyday incidents was thoroughly examined with regard to whether the patient practiced CAM in a given 12-hour unit and, moreover, what she experienced in response to CAM practice.

Incidents and Hassles Inventory (IHI). The Incidents and Hassles Inventory (IHI) is a semi-structured interview to assess psychosocial everyday incidents.²⁵ In addition to a list of 38 pre-defined everyday incidents (eg, time pressure at work, argument with spouse), the interview also deals with incidents mentioned spontaneously by the patient and with those noted by the patient in the DIARI that do not belong to the 38 pre-defined incidents. All incidents, including those regarding CAM practice, were examined in detail with the patient, exploring what she thought and did as they unfolded, her emotional response, the temporal specifics of incidents, the extent to which they were anticipated, persons involved, memories evoked, etc. Each weekly interview lasted approx. 1 hour and was recorded on audio cassette.

Both DIARI and interview data were used to construct the binary CAM time series. 12-hour units in which CAM techniques had been practiced were coded as "1", and 12-hour units in which no CAM techniques had been applied were coded as "0". The 12-hour documentations in the DIARI have proven useful for the exact chronological assignment of psychosocial incidents.

Telephone interview and Internet research. As already mentioned, the use of CAM techniques was not planned in advance of the study. Moreover, at the time of the study, neither the investigators nor the patient were aware that CAM techniques would later be evaluated for their stress

system effects. Thus, almost 9.5 years after completion of the study (January 21st, 2016), a telephone interview was conducted with the patient to retrospectively obtain study-relevant information on CAM practiced during the study period (ie, Jin Shin Jyutsu, music, physiotherapy, Tai Chi, energy healing). The following information was gathered:

- (1) The patient learned Jin Shin Jyutsu from a student of the well-known Jin Shin Jyutsu teacher, Petra Elmendorff.³⁷
- (2) The musical interventions refer to choir singing, singing alone at home and piano playing alone at home.
- (3) Once a week, Cornelia Döhle, a physiotherapist (German Association for Physiotherapy) specialized in “manual therapy,” “craniosacral techniques” and Shiatsu, treated the patient.
- (4) During and long before the study, the patient practiced Yang-style Tai Chi weekly at the Tai Chi School in Freiburg. This is a type of Tai Chi that goes back to Yang Lu-Chan (1799-1872).³⁸
- (5) During the study period, the patient attended a seminar on energy healing with Suzanne Michels, who had learned this technique from the International Network for Energy Healing (INEH).³⁹

Measurement of Mood, Irritation, and Mental Activity

The short version of the Eigenschaftswörterliste (3-Scale-EWL) is a German paper-pencil test with sufficiently high internal consistency.⁴⁰ It contains 28 adjectives that measure momentary emotional states in 3 categories: mood, irritation, and mental activity. The patient rated each adjective on a 4-point Likert scale (1=not at all; 2=a little; 3=quite; 4=very). Mood is captured via 4 positive (glad, good mood, happy, joyful) and 4 negative (depressed, sad, gloomy, worried) adjectives. The summary scores of each mood subcategory (positive, negative) range from 1 to 4 points and are calculated by averaging the single scores of the subcategories. The 3-Scale-EWL is suitable for process analyses. In the present study, the 3-scale EWL was included in the DIARI and completed by the patient in 12-hour intervals. The 3-scale EWL requires a few minutes to fill out.⁴⁰

Urinary Neopterin Measurements

The 55 urinary neopterin and creatinine concentrations were determined using high-performance liquid chromatography (HPLC) (Model ProStar 210 Solvent Delivery Module; Varian Associates, Palo Alto, CA). Urinary neopterin concentrations are expressed in micromoles per mole ($\mu\text{mol/mol}$) of creatinine to compensate for changes in urine density.²⁹ The 55 consecutive urine samples were measured in 1 single run. For each of the 5 independent

determinations, a new aliquot was used, and results were averaged to reduce variation of analytical performance.

Time Series Analyses

Urinary neopterin concentrations normally show circadian rhythms, with the largest amount of neopterin being released at about 10:00 p.m. and 6:30 a.m.⁴¹ This may result in false positive or false negative cross-correlations with other time series that also show rhythms. In order to take this into account, serial dependencies (eg, autoregressive processes, trends, cyclic, and seasonal components) were statistically controlled by the use of autoregressive-integrated-moving-average (ARIMA) modeling. An ARIMA model is characterized by 3 terms: p, d, and q, whereby p refers to the order of the autoregressive (AR) term. The AR part indicates that the evolving variable of interest is regressed on its own lagged (ie, prior) values. The term q is the order of the moving average (MA) term. The MA part indicates that the regression error is actually a linear combination of error terms whose values occurred contemporaneously and at various times in the past. The I (for “integrated”) indicates that the data values have been replaced with the difference (“d”) between their values and the previous values in order to stabilize the mean of a time series, that is make a series stationary. Stationarity with regard to the mean of a time series can also be achieved by removing a deterministic trend from the time series.⁴² When tests for constant variance indicated heteroskedasticity, a series was log-transformed.⁴³ Logarithmization of time series was also used to improve model specification. The final choice of the model was based on factors such as the serial independency of residuals (eg, Ljung-Box Test⁴⁴), information criteria (eg, RMSE, normalized BIC) and the statistical significance of model parameters.

For cross-correlational analysis, residuals generated from time series modeling were applied.⁴² Cross-correlational analysis, that is, the correlation between 2 random variables, made it possible to identify direction of effects, pattern of effects and temporal delays between variables. A significance level α of 0.05 was used for statistical analysis. Missing data in time series were corrected by linear interpolation. SPSS-TrendsTM 24.0 was applied for time series analyses.⁴⁵ Further details on the statistical analyses used in this study are described by Schubert et al.²⁶

Results

The time series of the present study cover a total of 28 days or 55 12-hour intervals ($N=55$). The positive mood time series had 1 missing value (at 12-hour unit 52); all other times series were complete. During the study period, the patient showed no signs of any disease that could have influenced immune activity (eg, infectious disease).

The patient practiced CAM during a total of 21 12-hour units: Jin Shin Jyutsu 3 times (1, 7, 52), music 7 times (2, 3,

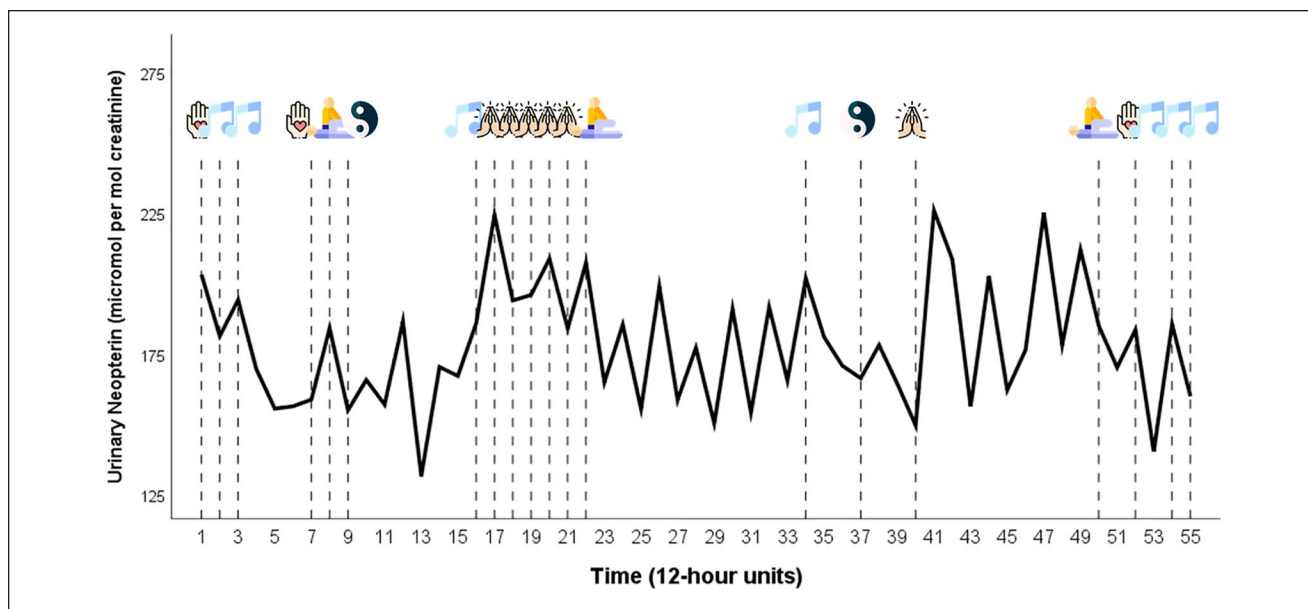


Figure 1. CAM techniques in temporal relation to urinary neopterin time series. The patient practiced CAM techniques during 19 of the 55 12-hour units, that is, 28 days (*x*-axis), Jin Shin Jyutsu 3 times (1, 7, 52), music 7 times (2, 3, 16, 34, 52, 54, 55), physiotherapy 3 times (9, 22, 50), Tai Chi twice (12-hour units 9 and 37) and energy healing 6 times (17, 18, 19, 20, 21, 40). As Tai Chi was the only CAM technique that the patient experienced as negative and physically stressful, it was not included in further statistical analyses. The *y*-axis shows urinary neopterin concentrations ($\mu\text{mol}/\text{mol}$ creatinine). During the study period, the patient collected her entire urine in 12-hour intervals (day portions from 8:00 a.m. to 8:00 p.m. and night portions from 8:00 p.m. to 8:00 a.m.). The neopterin time series starts with a night urine portion.

-  = Jin Shin Jyutsu
-  = music
-  = physiotherapy
-  = Tai Chi
-  = energy healing

(Icons taken from: <https://www.flaticon.com/de>).

16, 34, 52, 54, 55), physiotherapy 3 times (9, 22, 50), Tai Chi twice (12-hour units 9 and 37) and energy healing 6 times (17, 18, 19, 20, 21, 40) (Figure 1). On average, the patient applied a CAM technique every third 12-hour unit during the study.

Qualitative analysis revealed that Tai Chi was the only intervention during the course of the study that the patient described as negative and physically stressful. The patient assessed all other CAM techniques (Jin Shin Jyutsu, music, physiotherapy, energy healing) as positive (Table 1). Because of the patient's negative assessment, Tai Chi was not included in the CAM time series and thus not considered in the subsequent time series analyses.

The mean values of emotional states and urinary neopterin are as follows: positive mood 1.7 ± 0.5 (range: 1.0-3.5); negative mood 2.3 ± 0.8 (range: 1.3-4.0); mental activity: 1.5 ± 0.3 (range: 1.0-2.0); irritation 2.4 ± 0.6 (range: 1.6-3.4); urinary neopterin: $178 \pm 22 \mu\text{mol}/\text{mol}$ creatinine (range: 131-226).

The time series of urinary neopterin concentrations ($\mu\text{mol}/\text{mol}$ creatinine) is shown in temporal relation to CAM practice in Figure 1. The ARIMA models of the variables used in this study are the following: positive mood AR (1) ln; negative mood AR (1) ln; irritation MA (1); mental activity AR (4,1) ln; urinary neopterin MA (2) ln.

Figure 2a-e shows the cross-correlation functions between CAM practice (ie, Jin Shin Jyutsu, music, physiotherapy, energy healing) (leading variable) and emotional states (ie, positive mood [2a], negative mood [2b], mental activity [2c], irritation [2d]) as well as urinary neopterin concentrations (2e) (lagging variables). Specifically, CAM practice is followed by increases in the patient's positive mood during the next 12 hours (lag 0: $r = +.286$; $P = .034$) and by decreases in her positive mood after 72 to 84 hours (+lag 6: $r = -.329$; $P = .015$) (Figure 2a). Moreover, CAM practice is followed by decreases in the patient's negative mood during the next 12 hours (lag 0: $r = -.495$; $P = .0002$)

Table 1. Patient's Comments (English Translation) on CAM Practice as Recorded in the DIARI (Non-Italicized) and IHI (Italicized).

12-hour unit	CAM technique	Comment
1	Jin Shin Jyutsu	Jin Shin Jyutsu while lying awake
2	Music	Wonderful choir rehearsal in the evening
3	Music	Choir—singing—saw beautiful moon from the balcony
7	Jin Shin Jyutsu	Jin Shin Jyutsu—helped reliably with my stomach cramps + calms me
8	Physiotherapy	Very pleasant/beneficial/good physiotherapy session + lymph drainage, much more energy afterwards
9	Tai Chi	What I love (Tai Chi) + and what should do me good but then doesn't do me good
16	Music	Singing lesson, I always feel good afterwards
17-21	Energetic healing	<i>"Those weekends are always really extraordinary"</i> [12-hour unit 17] Meditation + mutual treatment in the seminar group -> great relaxation + "inner cooling down" [12-hour unit 18] Spent a very interesting, stimulating + relaxing day in the course for energetic (spiritual) healing. A lot of meditation, concentration, mutual treatment, beautiful human togetherness—very far away from everyday life [12-hour unit 20] Another seminar day, as beautiful, invigorating + interesting as yesterday
22	Physiotherapy	Physiotherapy at my friend Conny's—since then, foot, knee and + back are pain-free!
34	Music	<i>"I played—today, on Sunday, my husband wasn't here—music all day"</i>
37	Tai Chi	Tai Chi, see above
40	Energetic healing	Treatment at Suzanne's (spiritual healing teacher). Afterwards, I feel more free, bold + fit
50	Physiotherapy	Physiotherapy treatment + lymph drainage at Conny's with lively discussion
52	Jin Shin Jyutsu	Jin Shin Jyutsu helps me to overcome my deep exhaustion + to have some drive again
52	Music	"Practiced for choir + was happy with my progress, especially on the piano". On pieces with 4 sharps or with 5b, I had to give up sooner!
54	Music	Really magical choir practice in the early evening at our home. Extraordinarily beautiful, nice people, wonderful mix of voices—what great luck! Afterwards, I was completely relaxed, euphoric + optimistic. I'm happy that I have enough concentration for these partly very hard pieces!
55	Music	Choir continues to have an effect!

"5b" in the text refers to "5 flats".

and by increases in her negative mood 84 to 96 hours later (+lag 7: $r = +.317$; $P = .019$) (Figure 2b). Also, CAM practice is followed by increases in the patient's mental activity during the next 12 hours (lag 0: $r = +.268$; $P = .047$) and by decreases in her mental activity after 84 to 96 hours (+lag 7: $r = -.330$; $P = .014$) (Figure 2c). Cross-correlating CAM practice with the patient's irritation intensity reveals that decreases in irritation precede CAM practice by up to 12 hours (−lag 1: $r = -.274$; $P = .042$) (Figure 2d). In Figure 2e, the cross-correlation function between CAM practice and the patient's urinary neopterin concentrations reveals that CAM practice is followed by urinary neopterin level increases during the next 12 hours (lag 0: $r = +.304$; $P = .024$) and by decreases 36 to 48 hours later (+lag 3: $r = -.281$; $P = .037$).

Discussion

This integrative single-case study on a 49-year-old female breast cancer survivor suffering from CaRF and depression used both qualitative methods and time series analysis on 55 consecutive 12-hour measurements in order to explore the impact of CAM on emotional states and inflammatory activity in cancer. After specifying qualitatively (via interview and DIARI) those CAM techniques that the patient experienced as positive, that is, Jin Shin Jyutsu, music, physiotherapy, and energy healing (Table 1), time series analyses showed that episodically practicing these CAM techniques was followed by significant changes in psychological and immunological variables. These changes differed with regard to time delays and response patterns.

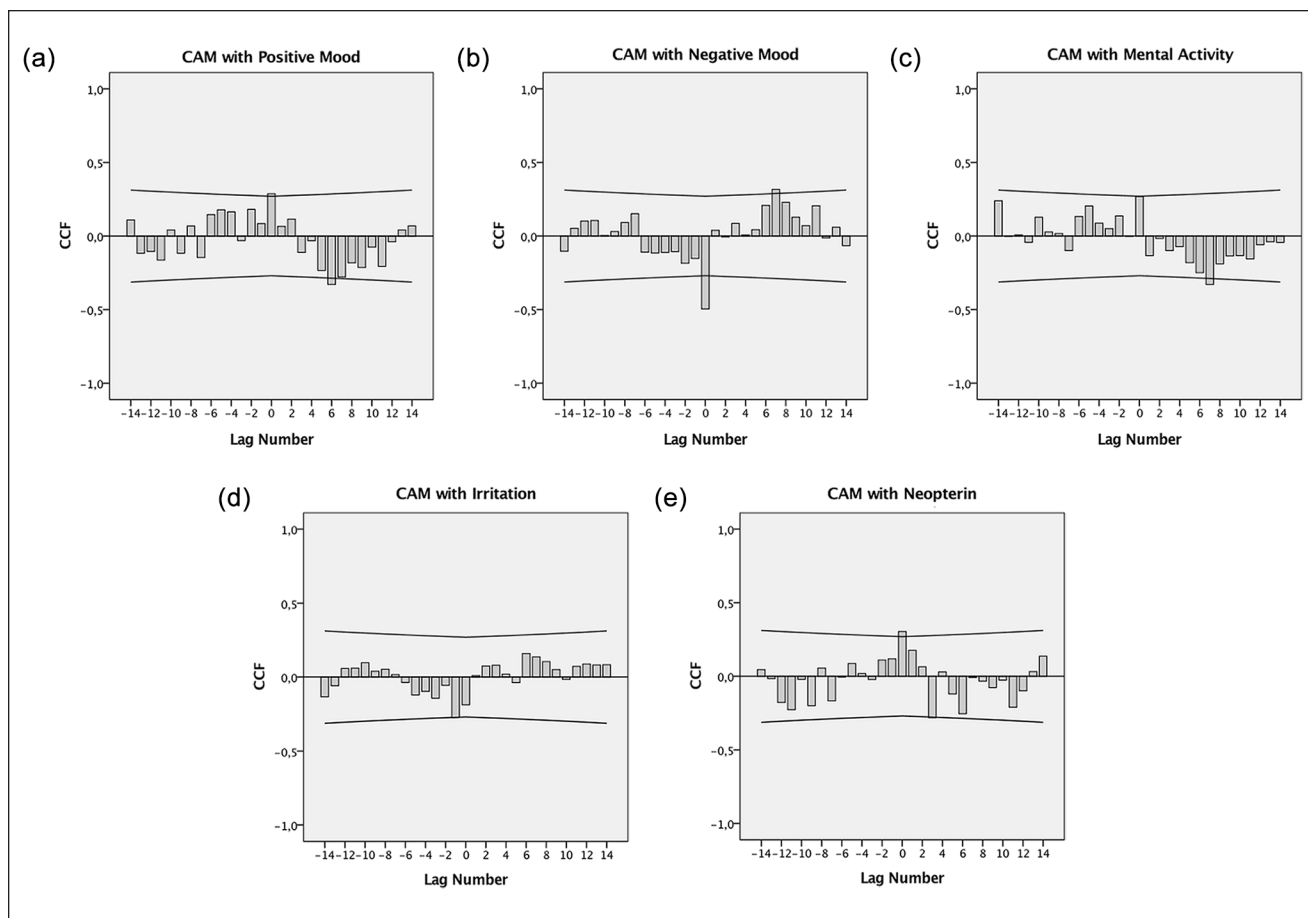


Figure 2. Cross-correlation functions (CCF) between CAM (ie, Jin Shin Jyutsu, music, physiotherapy, energy healing) and positive mood (a), negative mood (b), mental activity (c), irritation (d), and urinary neopterin (e). Each lag represents a time interval of 12 hours. Plots show the cross-correlation coefficients (bars) and the upper and lower limits of the 95% confidence intervals. A significance level of $P < .05$ was determined. Lag 0 on the x-axis signifies the time of a CAM event. A zero lag significance means that CAM is followed by another variable during the next 12 hours. A positive lag significance means that CAM is followed by another variable, whereas a negative lag significance means that another variable precedes CAM.

Cross-correlational analyses revealed that practicing CAM was followed by significant biphasic or cyclic response patterns in the patient's mood and mental activity. Specifically, following CAM practice, positive mood and mental activity first increased during the next 12 hours and then decreased a total of 72 to 84 hours (positive mood) and 84 to 96 hours (mental activity) later. Negative mood, by contrast, first decreased during the next 12 hours and then increased after a total of 84 to 96 hours following CAM.

While the cross-correlational findings on the patient's short-term positive emotional responses to CAM practice (ie, improved mood and higher mental activity within 12 hours) are verifiable in the interviews and DIARI data (see Table 1), the cross-correlational findings on her long-term negative emotional responses (ie, worsened mood and lower mental activity up to 96 hours later) are not mirrored in the qualitative data and might seem, at first sight,

counterintuitive. However, considering that affective dynamics in naturalistic situations can reveal the regulation of emotion in real time,⁴⁶ the long-term negative emotional response in this study can be more easily understood. In line with the control-process view,^{47,48} improved mood co-occurring with CAM practice may have served as a sensor indicating that the patient's goal, doing something good for her health, had been reached. However, the worsened mood several days after CAM practice may have been a signal to her that more effort would again be necessary in order to stay healthy, which may then have induced her to pursue further CAM practice. From a functional perspective, therefore, the patient's emotional cycle in response to CAM practice is continuous and ongoing and consists of a mixed feedback loop in which emotion is first up-regulated via positive feedback and then down-regulated through negative feedback.⁴⁶

Somewhat similar functional response patterns were also detected for the patient's irritation—although the relevant cross-correlation coefficients were not all significant. Specifically, preceding (anticipating) CAM practice, irritation decreased during the 12 hours before CAM. Then, following CAM, irritation increased—though not significantly—a total of 72 to 84 hours later (see Figure 2d). Normally, in life science, non-significant correlation coefficients are not considered valuable. However, the apparent cyclical behavior between CAM and irritation shows how important descriptive statistics—in addition to inferential statistics—can be to detect patterns in investigations relying on time series analysis.²⁶

In addition to cyclic changes in emotional states, this study also showed that CAM practice was followed by a significant cyclic immunological reaction. Specifically, urinary neopterin levels first increased on the day of CAM practice and then decreased after a total of 36 to 48 hours following CAM (see Figure 2e). This CAM-associated decline in the patient's neopterin may relate to her preceding emotionally positive response to CAM practice. In cancer, decreases in neopterin concentration reflect decreases in inflammatory activity, which is a healthy reaction and prognostically favorable.^{29,30} The patient episodically practiced CAM between breast cancer diagnosis and the study start, did so during the study and has continued with CAM since the end of the study. Thus, it may be speculated that the neopterin-reducing effects of CAM shown in this study made an important contribution to the absence of cancer recurrence and continues to positively influence the patient's long-term prognosis. This assumption is also supported by the patient's mean urinary neopterin concentration of 178 $\mu\text{mol/mol}$ creatinine during the study interval of 28 days. According to Murr et al⁴⁹ who found in healthy 46 to 55 year-old women a mean level of 147 + 32 μmol neopterin/ mol creatinine with an upper normal limit of 229, this mean level of our patient may be considered normal, thus indicating normal inflammatory activity and a good prognosis.³⁰

As already mentioned, this study was not an intervention study, and the patient followed her normal everyday routine without any external study-related guidelines or restrictions. As a result, we have 21 CAM events consisting of 5 different techniques (ie, Jin Shin Jyutsu, music, physiotherapy, Tai Chi, energy healing), ranging in frequency from 2 to 7 occurrences that are unevenly distributed throughout the study period (see Figure 1). Consequently, it was not possible to analyze each technique's efficacy separately. However, it should be kept in mind that CAM treatments not only consist of specific "verum" effects but also of unspecific "placebo" effects. The latter depend on a variety of patient-practitioner relationship factors such as the susceptibility of the patient to suggestion and the ability of the practitioner to instill trust.⁵⁰ Moerman describes the placebo effect (and its negative counterpart, the nocebo effect) as

meaning response—specifically, how people (subconsciously) react physiologically and psychologically to meaningful stimuli in the treatment of illness.⁵¹

We suggest that the cyclic course of emotional states and urinary neopterin levels observed in this study in reaction to CAM mirror meaning as a shared unspecific operating principle behind all of the CAM treatments experienced by the patient as positive. We base this interpretation on previous findings from integrative single-case studies showing cyclic stress system patterns in response to emotionally meaningful everyday incidents—regardless of whether these incidents were emotionally positive or negative and whether healthy or chronically ill individuals were investigated.^{52,53,26} Therefore, the finding of this study that CAM practice was related to cyclic psycho-immunological response patterns suggests that practicing CAM may also constitute emotionally meaningful incidents for this patient. From a mechanistic perspective, the meaning response associated with CAM practice may have been connected with recurrent cognitive, emotional and motivational adaptation processes reflected by a dynamic back and forth between CNS activity (eg, HPA axis, SNS) and peripheral immune changes, amounting to a biopsychosocial top-down-bottom-up reverberating feedback loop. In our patient, this mechanism was ultimately followed by a temporary decrease in urinary neopterin levels, that is, inflammatory activity^{29,30} and can be understood as the activation of the patient's self-healing capacities.

This study has several limitations. As the original investigation on which this study is based did not expect to analyze potential effects of CAM treatments, neither the interviews nor the DIARI explicitly targeted CAM, its application specifics or its meaning to the patient. In a subsequent interview, almost a decade after the end of the original study, additional information about the CAM methods applied was obtained from the patient. However, gathering information retrospectively entails the risk of possible gaps in memory and memory biases ("recall bias"⁵⁴). Thus, a certain degree of speculation remains as to whether the patient in this study experienced a psycho-immunological meaning response.

Furthermore, as mentioned above, Tai Chi—practiced on 2 days during the study period—was removed from the time series of CAM techniques because the patient described it as negative and physically stressful. It should be noted here, however, that the patient's reaction appears to have been circumstantial and not specific to Tai Chi. In fact, Tai Chi is widely recognized as an effective health-promoting technique⁵⁵; moreover, the patient stated that she generally experiences this technique as positive (see Table 1), suggesting that under different circumstances the patient would have profited from Tai Chi.

It might be argued that a generalization of results from single-case studies is only possible with sufficient replication across several individuals. This is partly correct. On the one hand, accumulation of integrative single-case studies

on CAM could indeed enlarge our understanding of how CAM therapies function in patients' lives and form the basis of testable hypotheses aimed at the improvement of CAM and integrative treatment.⁵⁶ On the other hand, however, a research approach with extraordinarily high ecological (external) validity such as the integrative single-case design legitimizes generalizations—not in the sense of a high number of cases but in the sense of a transferability of the results into a “real life setting.”⁵⁷

As to the interventional character of this investigation, we assume that it is not the strict control of contextual factors and the use of standardized intervention programs but the freedom of everyday life that permits us to access complex biopsychosocial realities in medical research. Here, we showed that, through the study of the free unfolding of an individual's everyday reality in space and time in combination with rigorous evaluation of qualitative data and time series analyses, deep insights into the biopsychosocial effects of treatments such as CAM interventions can be realized.

Conclusion

Through the episodic use of various CAM techniques, the breast cancer survivor under study may have actively contributed to her individual healing process: A complex biopsychosocial process in which cultural, social and subjective aspects (“meaning response”⁵¹) together with a reduction of inflammatory activity appears to have played an important role. This study shows that biopsychosocial research approaches such as the “integrative single case study,”²⁵ which investigates individuals in their “life as it is lived” reality and considers the effects of meaning, can methodologically grasp the complex mechanisms of medical interventions such as CAM practices.

Acknowledgment

We thank the patient of this study for her participation. BKK ProVita kindly supported the preparation of this work. Icons made by Freepik from www.flaticon.com.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This article was supported by the Innovation Committee of the Federal Joint Committee (G-BA) of the Federal Republic of Germany (funding number: 01NVF17045).

ORCID iD

Christian Schubert  <https://orcid.org/0000-0001-7100-0663>

References

- Engel GL. The need for a new medical model: a challenge for biomedicine. *Science*. 1977;196:129-136.
- Schubert C. Einführung. In: C Schubert, ed. *Psychoneuroimmunologie und Psychotherapie*. 2nd ed. Schattauer; 2015: 1-17.
- Tsigos C, Chrousos GP. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *J Psychosom Res*. 2002;53:865-871.
- Armaiz-Pena GN, Cole SW, Lutgendorf SK, Sood AK. Neuroendocrine influences on cancer progression. *Brain Behav Immun*. 2013;30:19-25. doi:10.1016/j.bbi.2012.06.005
- Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. *Clin. Cancer Res*. 2012;18:1201-1206.
- Dhabhar FS, Saul AN, Holmes TH, et al. High-anxious individuals show increased chronic stress burden, decreased protective immunity, and increased cancer progression in a mouse model of squamous cell carcinoma. *PLoS One*. 2012;7:e33069.
- Powe DG, Voss MJ, Zanker KS, et al. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. *Oncotarget*. 2010;1:628-638.
- Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull*. 2004;130:601-630. doi:10.1037/0033-2909.130.4.601
- Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. *Psychol Bull*. 2011;137:959-997. doi:10.1037/a0024768
- Marx J. Cancer research. Inflammation and cancer: the link grows stronger. *Science*. 2004;306:966-968.
- Swartzman S, Booth JN, Munro A, Sani F. Posttraumatic stress disorder after cancer diagnosis in adults: a meta-analysis. *Depress Anxiety*. 2017;34:327-339.
- Besedovsky HO, Rey AD. Physiology of psychoneuroimmunology: a personal view. *Brain Behav Immun*. 2007;21: 34-44.
- Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420:860.
- Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun*. 2007;21:413-427.
- Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9:46-56.
- Hou R, Baldwin DS. A neuroimmunological perspective on anxiety disorders. *Hum Psychopharmacol*. 2012;27:6-14.
- Ott M, Singer M, Hannemann J, Bliem HR, Schubert C. Wird mit onkologischen Erkrankungen vor dem Hintergrund psychoneuroimmunologischer Erkenntnisse aktuell angemessen umgegangen? *DZO*. 2016;48:144-151.
- Horneber M, Bueschel G, Dennert G, Less D, Ritter E, Zwahlen M. How many cancer patients use complementary and alternative medicine: a systematic review and

- metaanalysis. *Integr Cancer Ther.* 2012;11:187-203. doi:10.1177/1534735411423920
19. Lee SM, Choi HC, Hyun MK. An overview of systematic reviews: complementary therapies for cancer patients. *Integr Cancer Ther.* 2019;18:1534735419890029. doi:10.1177/1534735419890029
 20. Frass M, Strassl RP, Friehs H, Müllner M, Kundi M, Kaye AD. Use and acceptance of complementary and alternative medicine among the general population and medical personnel: a systematic review. *Ochsner J.* 2012;12:45-56.
 21. Black DS, Slavich GM. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. *Ann NY Acad Sci.* 2016;1373:13-24.
 22. Bower JE, Irwin MR. Mind-body therapies and control of inflammatory biology: a descriptive review. *Brain Behav Immun.* 2016;51:1-11. doi:10.1016/j.bbi.2015.06.012
 23. Witt CM, Barth J, Canella C. The future of complementary and integrative medicine research - international perspectives. *Forsch Komplementmed.* 2015;22:125-127. doi:10.1159/000381512
 24. Singer M, Bliem HR, Schubert C. Achtsamkeitsbasierte Therapieverfahren aus der Sicht der Psychoneuroimmunologie. *Ärztliche Psychother.* 2016;11:93-98.
 25. Schubert C, Lampe A, Rumpold G, et al. Daily psychosocial stressors interfere with the dynamics of urine neopterin in a patient with systemic lupus erythematosus: an integrative single-case study. *Psychosom Med.* 1999;61:876-882.
 26. Schubert C, Geser W, Noisternig B, et al. Stress system dynamics during "life as it is lived": an integrative single-case study on a healthy woman. *PLoS One.* 2012;7:e29415. doi:10.1371/journal.pone.0029415
 27. Schubert C. Soziopsychoneuroimmunologie-Integration von Dynamik und subjektiver Bedeutung in die Psychoneuroimmunologie. In: C Schubert, ed. *Psychoneuroimmunologie und Psychotherapie.* 2nd ed. Schattauer; 2015: 418-452.
 28. Haberkorn J, Burbaum C, Fritzsche K, et al. Day-to-day cause-effect relations between cellular immune activity, fatigue and mood in a patient with prior breast cancer and current cancer-related fatigue and depression. *Psychoneuroendocrinology.* 2013;38:2366-2372. doi:10.1016/j.psyneuen.2013.03.001
 29. Fuchs D, Weiss G, Reibnegger G, Wachter H. The role of neopterin as a monitor of cellular immune activation in transplantation, inflammatory, infectious, and malignant diseases. *Crit Rev Clin Lab Sci.* 1992;29:307-344.
 30. Sucher R, Schroecksnadell K, Weiss G, Margreiter R, Fuchs D, Brandacher G. Neopterin, a prognostic marker in human malignancies. *Cancer Lett.* 2010;287:13-22.
 31. Hüfner K, Oberguggenberger A, Kohl C, et al. Levels in neurotransmitter precursor amino acids correlate with mental health in patients with breast cancer. *Psychoneuroendocrinology.* 2015;60:28-38.
 32. Lanser L, Kink P, Egger EM, et al. Inflammation-induced tryptophan breakdown is related with anemia, fatigue, and depression in cancer. *Front Immunol.* 2020;11:249. doi:10.3389/fimmu.2020.00249
 33. Singer M, Burbaum C, Fritzsche K, et al. Subjective positive and negative sleep variables differentially affect cellular immune activity in a breast cancer survivor: a time-series analysis approach. *Front Neurol.* 2018;8:693.
 34. Schubert C, Hagen C. Bidirectional cause-effect relationship between urinary interleukin-6 and mood, irritation, and mental activity in a breast cancer survivor. *Front Neurosci.* 2018;12:1-7.
 35. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and pro-inflammatory cytokine activity in breast cancer survivors. *Psychosom Med.* 2002;64:604-611.
 36. Blamey RW, Ellis IO, Pinder SE, et al. Survival of invasive breast cancer according to the Nottingham Prognostic Index in cases diagnosed in 1990–1999. *Eur J Cancer.* 2007;43:1548-1555.
 37. Elmendorff P. Jin Shin Jyutsu. About me. Accessed November 24, 2020. https://petra-elmendorff.de/en/jsj_2.html
 38. Verheyden J. Taichifreiburg. Tai Chi Chuan: Geschichte. Accessed November 24, 2020. <http://taichifreiburg.de/geschichte/>
 39. Mit Liebe heilen. International Network for Energy Healing. Accessed November 24, 2020. <https://mit-liebe-heilen.de/lehrerinnen/suzanne-michels-2/>
 40. Becker P. Skalen für Verlaufsstudien der emotionalen Befindlichkeit. *Z Exp Angew Psychol.* 1988;35:345-369.
 41. Auzéby A, Bogdan A, Krosi Z, Touitou Y. Time-dependence of urinary neopterin, a marker of cellular immune activity. *Clin Chem.* 1988;34:1866-1867.
 42. Box GEP, Jenkins GM, Reinsel GC. *Time Series Analysis: Forecasting and Control.* Holden-Day; 1976.
 43. Woolridge JM. *Introductory Econometrics: A Modern Approach.* 4th ed. South-Western; 2009.
 44. Ljung GM, Box GEP. On a measure of lack of fit in time series models. *Biometrika.* 1978;65:297-303.
 45. IBM Corp. *IBM SPSS Statistics for Windows, Version 24.0.* IBM Corp; 2016.
 46. Hollenstein T. This Time, It's Real: Affective flexibility, time scales, feedback loops, and the regulation of emotion. *Emot Rev.* 2015;7:308-315. doi:10.1177/1754073915590621
 47. Carver CS, Scheier MF. Origins and functions of positive and negative affect: a control-process view. *Psychol Rev.* 1990;97:19-35. doi:10.1037/0033-295X.97.1.19
 48. Carver CS. Control processes, priority management, and affective dynamics. *Emot Rev.* 2015;7:301-307. doi:10.1177/1754073915590616
 49. Murr C, Widner B, Wirleitner B, Fuchs D. Neopterin as a marker for immune system activation. *Curr Drug Metab.* 2002;3:175-187. doi:10.2174/1389200024605082
 50. Hunter P. A question of faith. Exploiting the placebo effect depends on both the susceptibility of the patient to suggestion and the ability of the doctor to instill trust. *EMBO Rep.* 2007;8:125-128. doi:10.1038/sj.embor.7400905
 51. Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med.* 2002;136:471-476.
 52. Schubert C, Lampe A, Geser W, et al. Daily psychosocial stressors and cyclic response patterns in urine cortisol and neopterin in a patient with systemic lupus erythematosus. *Psychoneuroendocrinology.* 2003;28:459-473.
 53. Schubert C, Noisternig B, Fuchs D, et al. Multifaceted effects of positive incidents on urine cortisol and urine neopterin dynamics in a patient with systemic lupus erythematosus. *Stress Health.* 2006;22:215-227.

54. Catalogue of Bias Collaboration, Spencer EA, Brassey J, Mahtani K. Recall bias. In: Catalogue Of Bias. Published 2017. Accessed November 24, 2020. <https://catalogofbias.org/biases/recall-bias/>
55. Zeng Y, Luo T, Xie H, Huang M, Cheng ASK. Health benefits of qigong or tai chi for cancer patients: a systematic review and meta-analyses. *Complement Ther Med*. 2014;22:173-186. doi:10.1016/j.ctim.2013.11.010
56. Yin RK. *Case Study Research and Applications: Design and Methods*. 5th ed. Sage; 2014.
57. Mayring P. *Einführung in Die Qualitative Sozialforschung*. 5th ed. Beltz; 2002.