Integrative and complementary therapies for patients with advanced cancer

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Abstract: In integrative medicine, well-being is emphasized, and in palliative care, quality of life (QOL) is a similar concept or goal. Both can occur despite advanced cancer. Integrative medicine serves to combine the best of alternative, complementary and conventional therapies to optimize well-being and QOL, whether or not a person is at the end of their life. When integrative medicine is combined with palliative care modalities, the toolbox to provide symptom control and well-being or QOL is increased or broadened. Palliative care and integrative medicine are best provided early in the trajectory of illness such as cancer, and increase in amount as the illness progresses toward end of life. In cancer care, symptoms of the cancer, as well as symptoms produced by cancer therapies, are addressed with conventional and integrative therapies. Goals of care change as the disease progresses, and a patient's unique situation creates a different balance of integrative and conventional therapies. Integrative therapies such as music, aromatherapy, and massage might appeal to more patients than more specific, less common integrative therapies that might be more expensive, or seem more unusual such as Ayurvedic medicine and energy modalities. Each person may be drawn to different integrative modalities depending on factors such as cultural traditions, beliefs, lifestyle, internet information, advice from family and friends, books, etc. This review focuses on how integrative and complementary modalities can be included in comprehensive palliative care for patients with advanced malignancies. Nutrition and movement, often neglected in conventional treatment strategies, will also be included in the larger context of integrative and palliative modalities. Both conventional and integrative modalities in palliative care help patients live with empowerment, hope, and well-being no matter how long their lives last. A comprehensive review of all integrative and complementary therapies is impossible given the enormous diversity in this area. This review will concentrate on modalities such as nutrition, movement, music, aromatherapy, massage, select supplements, and acupuncture that have been researched in cancer survivors. Many of these modalities are quite effective for a number of symptoms in palliative care and have been studied in non-cancer populations. Resources for further study will also be included.

Keywords: Integrative medicine; integrative palliative care; integrative cancer care; integrative oncology care; palliative care in oncology

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Introduction

One in four deaths is due to cancer, and the lifetime probability of developing cancer is 45% for men and 38% for women. Lung, prostate, breast and colorectal cancers account for 48% of cancers. Palliative care is especially needed in the care of these patients (1). Palliative care, combined with integrative holistic medicine and conventional cancer care, can create a very effective approach to treating the whole person with cancer. This integration of care modalities addresses all appropriate treatments of the cancer, alleviating the challenging symptoms of cancer and its treatment, as well as helping
patients thrive rather than merely survive their cancer journey. In integrative medicine, well-being is emphasized, and in palliative care, quality of life (QOL) is a similar concept or goal. Both can occur despite advanced cancer. Integrative medicine serves to combine the best of alternative, complementary and conventional therapies to optimize well-being and QOL, whether or not a person is at the end of life. When integrative medicine is combined with palliative care modalities, the toolbox to provide symptom control and well-being or QOL is increased or broadened. Palliative care and integrative medicine are best provided early in the trajectory of illness such as cancer, and increase in amount as the illness progresses toward end of life. Goals of care change as the disease progresses, and a patient’s unique situation creates a different balance of integrative and conventional therapies. This review focuses on how integrative and complementary modalities can be included in comprehensive palliative care for patients with advanced malignancies.

Higher quality integrated cancer services can result in cost savings and can enhance cancer care. In palliative care research, it is recognized that higher costs and more conventional interventions do not necessarily increase the quality of care and often decrease it with unnecessary interventions with their own adverse effects (2). Inpatients of the oncology unit at Beth Israel Medical Center were part of an integrative medicine study called the Urban Zen Initiative. This included yoga therapy, holistic nursing techniques and attention to a healing environment. Cost data was analyzed via the electronic medical record and cost database. Eighty-five patients were in the non-intervention group and 72 in the intervention group. Researchers found that the integrative medicine group used fewer medications for symptoms, which resulted in substantial cost savings (3). In another retrospective cohort study of cancer survivors, those who used complementary and alternative medicine (CAM) therapies combined with conventional therapies were compared with those who did not use CAM. Baseline characteristics from a survey were compared with measurements from a chart review six months later. Results indicated that infections and hospitalizations were significantly reduced with CAM use (4). Many CAM therapies such as music, aromatherapy, exercise, relaxation, and mindfulness practices are inexpensive, accessible, effective, and easily incorporated into holistic and integrated treatment plans in conventional cancer centers and in palliative care services.

In a study of 17 patients who use CAM and conventional modalities and 20 alternative practitioners, themes of holism, empowerment, access and legitimization emerged from the analysis of semi-structured interviews. Conventional modalities were often more accessible to those who had insurance and were often more socially legitimate but often left patients disempowered with fragmented care. CAM modalities, because they were often paid out of pocket, felt less accessible, less legitimate by conventional medicine standards, but were more holistic and empowering. All who participated advocated for the integration of both conventional and CAM approaches (5).

Integrative and complementary modalities are commonly used by patients with advanced malignancies but often not reported to conventional medicine practitioners. Reasons for this vary considerably, and conventional practitioners may consider integrative modalities as interfering with conventional therapies, ineffective, a source of false hope, poorly researched, or harmful. Many practitioners also question the quality of research done on integrative modalities. Resources such as Inspire Health, an organization that provides quality reviews of the latest research in integrative cancer care, do provide patients and practitioners important evidence based information in addressing concerns of patients such as symptom management from advanced cancer and cancer treatments. Uninformed use of CAM therapies such as using an herb with a chemotherapy agent that interacts negatively with that herb can lead to toxicities of the conventional drug, or render it less effective. Who will inform the patient? Oncologists, palliative care practitioners, integrative health practitioners, and other health professionals can incorporate evidence based CAM modalities into their palliative and cancer care, and serve patients in a more open-minded and empowering way. If patients are doing their own research, clinicians can invite them to share their evidence and critically examine their data and come to a plan of care that is safe and effective. Left on their own, patients especially with cancer, are vulnerable to anecdotal, non-evidence based claims for CAM modalities that are potentially useless, expensive and harmful, and they may not be directed to sources of information on CAM modalities that are effective and more appropriate for a particular indication. The Society of Integrative Oncology has developed guidelines on evidence-based integrative oncology practice (6,7) (Table 1).

Integrative modalities increase the number of available options in the palliative care toolbox to treat patients with advanced cancer. The plan of care meetings common in palliative care can include queries on what patients feel are important in their cancer care, and this may include
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integrative modalities. A comprehensive review of all effective integrative and complementary therapies is impossible given the enormous diversity in this area. This review will concentrate on modalities such as nutrition, movement, mind-body modalities, music, aromatherapy, massage, select supplements, and acupuncture that have been recently researched in cancer survivors to give readers the most up to date research findings. Many of these modalities are quite effective for a number of symptoms in palliative care and have been extensively studied in non-cancer populations. CAM modalities used in relieving common symptoms addressed in palliative care are numerous and include systematic reviews of useful research in the Cochrane database and in peer reviewed journals (Table 2).

**Nutrition**

The American Cancer Society convened a panel of experts to review the research on nutrition and exercise for cancer survivors. Their first report and guidelines were published in 2006 and updated in 2012. Overall, the guidelines recommend maintaining a healthy weight, engaging in regular exercise including movement and strength training, and eating a diet high in fruits, vegetables and whole grains. Regular exercise may reduce cancer recurrence and cancer related mortality, increase QOL, decrease fatigue, anxiety, depression, and increase muscle strength and tone, and fitness. The guidelines also provide cautions about exercise during cancer treatment, such as avoiding pools and exercise in public places when immune deficient, avoiding chlorine exposure to irradiated skin, and paying special attention to balance if experiencing peripheral neuropathy. Food sources of nutrients are usually superior to supplement intake, and supplements not adequately found in foods such as vitamin D need to be carefully supplemented. The guidelines cover specific cancers and often-asked questions about controversial topics such as supplements. This is a well referenced evidence-based resource for patients and clinicians (8). Despite the existence of a large evidence-based literature on the benefits of healthy diet in cancer survivors, in one study, not one patient of 40 recruited received information from conventional clinicians on healthy eating (9).

A study by Zick et al. reported in 2013 examined associations of diet and fatigue in cancer survivors; those that had higher intake of whole grains, vegetables, particularly green leafy vegetables and tomatoes, reported less fatigue than those that had lower intake of these foods (10). Cruciferous vegetable intake in a 2012 study by Richman et al. decreased progression of prostate cancer (11).

Soy food intake in patients with breast cancer has in the past been controversial, but a number of studies more
recently have shown a protective effect in breast cancer patients reducing both mortality and recurrence of cancer (12,13). In a study of soy food consumption of >10 mg isoflavones in breast cancer survivors from data of U.S. and Chinese women, there was a nonsignificant reduction in cancer related mortality but significant reduction in risk of recurrence (14).

A high fat dairy diet was associated in one study of breast cancer survivors with increased cancer and non-cancer mortality, but low fat dairy had no effect on mortality (15). In 4,577 patients with non-metastatic prostate cancer, intake of animal fat and trans fats increased all cause mortality. Richman et al. reported that replacing 10% of animal fat with vegetable fat reduced the risk of developing lethal prostate cancer (16). In another study of milk fat content, ingestion of whole milk was associated with a higher risk of prostate cancer mortality and a higher incidence of more aggressive and fatal prostate cancer, while skim or low fat milk was associated with greater risk of non-aggressive prostate cancer. Increased intake of dairy foods was associated with increased prostate cancer incidence (17). Intake of processed meats increases the recurrence, mortality and metastatic activity of colorectal cancer (18).

**Exercise and movement**

Patients with cancer are often not encouraged to engage in exercise during cancer treatment, but the positive effects on QOL, weakness, fatigue and mood are documented in a number of studies.

In a 10-year longitudinal study of post-treatment breast cancer patients, pain was significantly reduced in patients who maintained regular physical activity and an ideal body weight, as opposed to those women who had a weight gain of >5%, who were obese or overweight, and had a sedentary lifestyle (19). In one small study of patients with non-small cell lung cancer, eight weeks of aerobic exercise training decreased fatigue and dyspnea, and increased exercise capacity even in patients with higher QOL (20). In Taiwanese lung cancer patients, light to moderate physical activity improved QOL during active treatment compared with sedentary patients. There were no significant differences in QOL in patients not in active treatment (21). A home based 8-week exercise program for post-mastectomy breast cancer patients with lymphedema showed a significant reduction in lymphedema and increase in QOL (22). Breast cancer patients in one study who exercised more had fewer symptoms, and patients that were more sedentary had higher rates of shoulder limitations, chest wall pain, weight gain, lymphedema, and breathlessness (23). An exercise intervention in a randomized controlled trial (RCT) of patients with breast cancer showed an increase in physical activity and more positive mood. These positive results persisted 60 months after the intervention (24). In a systematic review of 40 exercise interventions, a small overall decrease in depressive symptoms was found. Among cancer survivors, this response was greater depending on the amount of exercise; more was better than less. Improvements were greater for breast cancer patients, cancer survivors 47-62 years, and when exercise sessions were supervised (25).

Decreased functional capacity, weakness and fatigue, which lead to poor QOL, are common issues in patients with cancer or in cancer treatment. The Danish Head and Neck Cancer Group found that 12 weeks of progressive resistance training helped to build lean body mass, increased functional capacity and improved QOL (26). Another study of a home based light exercise program for patients after thoracotomy for lung cancer showed improvements in cancer related fatigue (27). A recent Cochrane Review also supported the findings that exercise can relieve cancer related fatigue (28). In another systematic review, Grade A evidence was found for exercise improving endurance, QOL, and reducing fatigue in prostate cancer patients. Grade B evidence exists for improving muscle mass, strength, functional capacity, health, social and physical QOL (29). The UW WELL-FIT program of aerobic exercise, strength training, and stretching in a supervised setting, demonstrated improved physical function and QOL in patients undergoing active cancer treatment (30).

Dragon boat racing, a popular team activity among cancer patients, especially breast cancer patients, helps improve QOL, fatigue, functional capacity, emotional and spiritual well-being (31).

In one small study of tai chi/qigong training, cancer survivors had increased shoulder mobility, strength and functional well being than the control group without the training (32).

A meta-analysis of 13 RCTs of yoga in cancer survivors documented significant reductions in distress, anxiety, and depression; moderate reductions in fatigue; moderate increases in social and emotional function, and QOL; and a small increase in functional well-being (33). Bower et al. also showed a reduction in fatigue in breast cancer survivors in a yoga program (34). Yoga breathing or pranayama can assist cancer patients during chemotherapy with sleep, anxiety,
and QOL (35).

One novel approach for increasing fruit and vegetable intake, increasing physical activity, agility, strength, and endurance is gardening for cancer survivors. In a study reported by Blair et al. in 2013, a master gardener mentor was paired with a cancer survivor for 1 year. The intervention included planting gardens, harvesting plants, and troubleshooting gardening problems (36).

**Herbs and supplements**

Herbs and supplements may be useful for a number of symptoms that occur with cancer treatment such as chemotherapy or radiation therapy. A key resource for assessing whether an herb or supplement may interfere with a particular chemotherapy agent or radiation therapy is the text “The definitive guide to cancer: an integrative approach to prevention, treatment, and healing” by Alschuler and Gazella. Some botanicals may interfere with the metabolism and action of chemotherapeutic agents such as taxanes, platinum-based drugs, cyclophosphamide, doxorubicin, etoposide, and irinotecan. Herbs and supplements might increase or decrease the action of a chemotherapeutic drug, by causing toxicity if too much drug becomes available, or becoming less effective if the drug’s metabolism is increased. Botanicals generally do not affect radiation therapy, but antioxidant supplements may or may not interfere with the action of radiation or chemotherapy. Antioxidants in food are not a concern (37). Frenkel et al. and the organization, The Society of Integrative Oncology, have created an evidence-based document on herbs and supplements such as curcumin, glutamine, vitamin D, Maitake mushrooms, fish oil, green tea, milk thistle, Astragalus, melatonin and probiotics, found to be most beneficial in cancer care. This document is recommended for a more complete review of these beneficial herbs and supplements (6). Many of our patients with advanced malignancies or who are elderly may be indoors due to illness, or cancer treatment effects such as weakness or fatigue. Vitamin D levels in this population may be low and put patients at risk for complications of vitamin D deficiency such as immune deficiency, fatigue, decreased bone mineralization, muscle pain, and weakness. One study found that 79.5% of patients with advanced breast cancer were vitamin D deficient (<30 ng/mL 25 hydroxy-vitamin D level) and at the end of neoadjuvant chemotherapy, 97.4% of patients were deficient (38). In a study of colorectal patients given 2,000 units of vitamin D3 daily, a rise of >10 nm/mL in 25-hydroxy vitamin D levels was found in 92% of chemo free patients versus 39% of patients undergoing chemotherapy. It was hypothesized that chemotherapy can attenuate the effects of vitamin D supplementation (39). Optimal levels for serum vitamin D levels are controversial. In a 9-year [1991-2000] follow-up analysis of the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994), a serum 25-hydroxy vitamin D level of 81 nmol/L was the nadir level of all-cause mortality with higher and lower levels of vitamin D showing a J shaped association of higher levels of all-cause mortality. This association held up for ages 20-64 years, and in non-Hispanic whites, but not in the elderly (40). Vitamin D levels in the highest normal quartile increased survival in patients with breast, colon, lung cancers and lymphoma (41). Suggested dosages are 800-2,000 units daily, and dosing can be checked with a 25-hydroxy vitamin D level to insure patients are not deficient or toxic according to lab reference values.

The use of antioxidant supplements during chemotherapy and radiation therapy in cancer patients remains controversial since theoretically antioxidants can decrease the effectiveness of these conventional therapies by neutralizing the cancer-damaging free radicals caused by these therapies. One study showed that breast cancer and chemotherapy decreased antioxidants enzymes and glutathione significantly. Women in the study who received 500 mg of vitamin C and 400 mg of vitamin E had more normal levels of antioxidant enzymes, less DNA damage, and more normal glutathione levels (42). The life after cancer epidemiology (LACE) study demonstrated that 81% of patients with breast cancer used antioxidant supplements after diagnosis. Among these women, those who used vitamin C or E had a lower rate of recurrence of cancer, and vitamin E users had lower all cause mortality. Those who used mixed carotenoids did not, and had an increase in recurrence (43).

Glutamine is protective for the upper and lower gastrointestinal (GI) tracts. Patients taking 15 grams of oral glutamine three times daily versus a placebo group had significantly less severe diarrhea caused by radiation therapy. No patients had severe diarrhea in the glutamine treated group, versus 69% of patients in the placebo group (44).

In another RTC, selenium twice daily was found to significantly decrease the severity and duration of mucositis in patients undergoing high dose chemotherapy and stem cell transplantation for leukemia (45). Two percent calendula gel can also decrease the intensity of oral mucositis in patients with head and neck cancers (46).
application of honey can also improve radiation-induced oral mucositis in head and neck cancer patients. This was shown in two studies (47,48).

Vitamin E 800 units per day can help prevent radiation induced salivary gland dysfunction in patients undergoing single dose radiation therapy for thyroid cancer (49). Probiotics, in a meta-analysis of six studies and systematic review of ten, significantly decreased radiation induced-diarrhea, and loperamide use decreased as well (50). Probiotics used peri-operatively during colectomy for colorectal cancer decreased post-operative infection (51).

Ginger is a botanical traditionally used for nausea and vomiting from a number of causes. It is efficacious for nausea associated with chemotherapy. Its mechanism of action is unknown (52). This herb is consumed as a tea (boiling ginger root in water), ginger root extract 500-1,000 mg every 4-6 hours as needed, or eating 1 teaspoon or 5 grams of crystallized ginger every 2-3 hours as needed. Too much can cause heartburn (53). In a large RTC of ginger at various doses versus placebo, ginger at the dose of 0.5-1 mg daily gave optimal effective control of chemotherapy-induced nausea (54,55).

Curcumin taken at dose of 6 grams a day significantly decreased radiation dermatitis in breast cancer patients (55). Calendula cream applied several times a day reduced radiation dermatitis in breast cancer patients (56).

Life review and cognitive/behavioral modalities and mindfulness-based-stress-reduction program (MBSR)

Psychological, social and spiritual health assists patients in thriving in their cancer journeys, as opposed to merely surviving. Psycho-oncology is a growing field with more cancer centers offering these services. This area of care includes cognitive behavioral interventions (either group or individual), relaxation techniques, breath work, mindfulness meditation, peer support groups, and prayer. Since so many cancer centers now offer these supportive services, the boundaries between integrative, complementary and conventional modalities are blurred. In a study of newly diagnosed multiple myeloma patients, those with depression and younger in age preferred psychosocial interventions such as peer support, relaxation techniques, and counseling (57). One study compared aromatherapy and massage with cognitive behavioral therapy (CBT) in a variety of cancer patients receiving conventional cancer care. Patients preferred the aromatherapy/massage intervention, and both interventions had similar improvements on depression, mood and anxiety scores (58). A brief mindfulness based CBT improved sexual functioning and sexual health in women with gynecological cancer (59).

One study using a mindfulness-based-stress-reduction program (MBSR) with breast cancer patients showed an increase in coping, healthy relationships, calmness, peacefulness, and acceptance (60). In another study of patients with breast cancer who are post surgery, chemo and radiation therapy, MBSR improved mood, QOL and well-being (61). MBSRs and mindfulness based cognitive therapy decrease anxiety and depression in breast cancer survivors (62). In one study of prostate cancer patients, an 8-week group cognitive behavioral intervention improved psycho-sexual well-being in patients following radical prostatectomy (63). In a pilot RCT of terminal cancer patients, brief CBT tailored to the issues most relevant to patients significantly reduced anxiety. This modality worked on relaxation skills, coping with concerns of cancer, and pacing activity (64). In another study using cognitive based stress management, prostate cancer survivors, in a 10-week group program, had increased levels of emotional well-being. This occurred even in the participants experiencing sexual and urinary dysfunction (65).

In rural and underserved populations without access to in-person support groups and emotional support services, online professionally lead support groups can also be beneficial (66). One study found that men prefer online communication in larger groups, and women prefer same gender, more intimate social support groups (67).

Dignity-enhancing therapy is a modality pioneered by Dr. Harvey Chochinov in Canada and used within palliative care. In his interviews of patients that had advanced cancer, he found that loss of dignity was common in these patients. A dignity model emerged from the research, and a dignity-enhancing intervention was created from the model which includes a brief life review interview guided by a trained interviewer. The interview is then transcribed and edited into a generativity document that can help not only the patient with emotional, psychological and spiritual issues, but also family and friends. In the beginning, this intervention was used with people in hospice nearing end of life. Although acceptability of the intervention and perceived benefit are measured in non RCTs, effect on outcome measures is less than robust in randomized control trials of the intervention (68-71).

Other studies have focused on advanced cancer patients. One RTC found that the dignity therapy increased hope in advanced cancer patients. Both the intervention and control
group scored low on dignity related distress, and there was no significant change in both groups; however, the intervention group scored higher on hope at one and four week follow up, but the control group did not. The groups were not significantly different on measures of anxiety, depression, QOL or other palliative care measures (72). One pilot study of advanced cancer patients and life review combined with online educational resources found the interview and receipt of an edited life story was helpful and meaningful. Most participants that were older than 70 years did not use the online resources (73). In a RTC of a dignity-enhancing life review combined with online support, cancer patients in the intervention group had a greater sense of peace (74).

Aromatherapy and essential oils

In a RCT of spearmint and peppermint oils in the treatment of chemotherapy-induced nausea and vomiting, these essential oils were significantly effective in reducing emetic events without adverse effects. Cost of overall treatment was decreased with essential oil use over the placebo or control, conventional treatment groups (75).

Massage

Massage may help cancer patients with reductions in anxiety, pain, and nausea. No effect on depression was found in a Cochrane Review on the topic of massage in cancer patients (76). In a population of veterans with cancer, massage provided by personal caregivers (81% spouses, 78% female), decreased pain, stress, anxiety, and fatigue. A total of 27 dyads of patient/caregiver were recruited, and 11 dyads completed the study. Attrition reported was due to caregiver burden. Massage was taught with video and written instructional materials, and done weekly by caregivers. Patients reported high levels of satisfaction with this touch therapy (77).

Acupuncture

At the Sao Paulo Cancer Institute, 183 patients were enrolled in an acupuncture study with 30% receiving active treatment with chemotherapy or radiation, 16% receiving hormonal treatment, and 55% in remission. Patients’ main symptoms were cancer pain, chemo-toxicity, lumbar pain, chronic postoperative pain. Acupuncture treatment significantly reduced the mean symptom severity scores from 7.04 to 2.56 (P<0.001) (78).

In a study of 33 patients with breast cancer related lymphedema of the arm, acupuncture significantly reduced arm circumference and was safe (79). Acupuncture can also reduce hot flashes and sleep disturbance in breast cancer survivors (80).

In 36 patients with postsurgical gastroparesis in abdominal cancers, 27 were cured, 6 improved and 3 not improved, with a combination of acupuncture, moxibustion, and cupping (81).

In a study of patients undergoing radiation therapy for nasopharyngeal cancer, acupuncture during radiation therapy reduced xerostomia and improved QOL (82).

Music

A Cochrane systematic review of music therapy in cancer patients found that music has positive effects on anxiety, pain, mood and QOL measures. There was no evidence to support positive effect on relief of depression (83).

Summary

Patients with advanced malignancies are best served by using an integrated, holistic, person centered approach using conventional and CAM therapies. The boundaries between CAM therapies and conventional therapies are often blurred especially as CAM therapies, such as vitamin D, accumulate scientific, evidence based research to demonstrate their usefulness even to those conventional practitioners cautious about their use. Nutritional and movement interventions with a plethora of quality research demonstrating positive outcomes for patients, are still not readily incorporated into all conventional oncology care. Palliative medicine can provide the bridge to patients with advanced malignancies to receive integrative services that provide higher QOL, decreased symptom burden, emotional and spiritual well being, hope, empowerment, reduced recurrence and mortality in some cancers, lower overall costs of care, and increased completion of conventional treatment sometimes not possible due to symptom burden and adverse effects. It is also our responsibility to discuss possible adverse effects of some CAM therapies when combined with certain conventional therapies. The balance of CAM and conventional therapies will continue to depend on the receptivity of individual patients, families, practitioners and health system priorities, and ongoing research efforts. CAM and conventional modalities can be combined in potentially synergistic ways to decrease the amount of medication needed to treat a symptom such as anxiety when a modality
such as music or meditation is also used. Palliative care practitioners, with open hearts and open minds, must be guided by evidence, creativity and person centered care.

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