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Acupuncture for Chemotherapy-Associated Cognitive Dysfunction: A Hypothesis-Generating Literature Review to Inform Clinical Advice

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There is an emerging consensus that between one fifth and one half of breast cancer patients experience chemotherapy-associated cognitive dysfunction. Research shows that patients with cancer are often interested in acupuncture for symptom relief. A clinical question thus arises: What should physicians advise their patients regarding the use of acupuncture to alleviate or ameliorate chemotherapy-associated cognitive dysfunction? The authors review and synthesize 2 bodies of relevant research literature: (1) the developing literature on the etiology and nature of chemotherapy-associated cognitive dysfunction and (2) the literature concerning acupuncture for neurological diseases and psychological issues. There is evidence that acupuncture may be effectively used to manage a range of psychoneurological issues, some of which are similar to those experienced by patients with chemotherapy-associated cognitive dysfunction. The evidence of efficacy is more promising for psychological than neurological conditions. Given evidence of possible efficacy combined with evidence of demonstrated safety, we suggest that physicians should support patient decisions to use acupuncture services for chemotherapy-associated cognitive dysfunction, especially given the lack of proven alternatives.

Keywords: *chemotherapy-associated cognitive dysfunction; acupuncture; neurological disorder*

Researchers have consistently demonstrated cognitive dysfunction in a substantial minority of patients with cancer¹⁻⁵; indeed, a recent review notes that 15% to 50% of patients with breast cancer may have cognitive dysfunction during and/or after chemotherapy.⁶ Reliable knowledge about the etiology, significance, and duration of chemotherapy-associated cognitive dysfunction is still developing as researchers begin to overcome a variety of research problems such as limited-sized samples, lack of baseline assessment, and failure to control for confounding variables such as hormonal factors.⁷ Without a doubt, however, neuropsychological issues are a problem for patients with

cancer and survivors—a conclusion reached in 2 prospectively designed longitudinal studies of cognitive dysfunction among women undergoing adjuvant chemotherapy for breast cancer,^{1,8} as well as a meta-analysis finding consistent adverse effects on executive function, verbal memory, and motor function.⁹ Physicians, and more generally clinicians, have to deal with the presence of cognitive difficulties in patients with cancer and survivors, even though there is a lack of evidence showing treatment options to be effective, as recently pointed out in an Institute of Medicine (IOM) report on cancer survivors.¹⁰

One solution that has not yet been explored is acupuncture. Cohen et al¹¹ point to evidence suggesting a skilled practitioner could use acupuncture to relieve a substantial variety of chemotherapy-induced side effects, including pain, fatigue, nausea/vomiting, xerostomia, and mood disorders. As of yet, there have been no clinical trials on the use of acupuncture for cognitive dysfunction. Furthermore, no one has reviewed the scientific literature on acupuncture to ascertain if it might be useful in treating and relieving chemotherapy-associated cognitive dysfunction. We do so, framing our findings within an evidence-based conceptual framework that physicians may employ to advise patients with cancer about the use of acupuncture and other complementary and alternative medicine (CAM) modalities to treat specific symptoms.¹²

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Chemotherapy-Associated Cognitive Dysfunction

Chemotherapeutic regimens are set at doses designed to kill cancer cells throughout the body, and there are frequently a variety of side effects such as fatigue, pain, and nausea and vomiting. Chemotherapeutic regimens are also associated with cognitive dysfunction¹³ that could involve a variety of psychological symptoms, including anxiety, depression, withdrawal, anger, hostility, survivor guilt, sleep difficulties, anorexia, agitation, and treatment noncompliance (avoidance of treatment-related reminders).¹⁻¹⁰ Patients in cancer support groups frequently discuss this topic with much concern, referring to “chemo-brain” or “chemo-fog.”¹⁴ A recent meta-analysis provides data showing small to moderate dysfunctions at an aggregate level in the domains of psychomotor function, attention, executive function and memory, and greater dysfunctions (although with less power) in the domains of language and spatial function.¹³ There remain substantial and significant gaps of understanding about the mechanisms, types, severity, and duration of chemotherapy-associated cognitive dysfunction,¹⁵ some of which are heatedly debated.

One area of controversy concerns the claim that chemotherapy-associated cognitive dysfunction results, at least in part, from structural damage in the central nervous system. Matsuda and colleagues¹⁵ pointed out that several pharmaceutical agents employed in chemotherapy regimens are neurotoxic, including 5-FU, which is known to directly damage Purkinje cells, as well as docetaxel and paclitaxel, which are considered to cause damage to sensory functions in the neurological system. The recently published IOM report on cancer survivors summarizes possible cognitive sequelae associated with chemotherapy (Table 1). Nonetheless, the issue remains contentious, and the field awaits carefully designed longitudinal studies using effective and sensitive imaging tools, such as positron emission tomography investigation, that specifically document the development of adverse changes to the structure of the neurological system that can be causally linked to chemotherapy.¹⁵

Along with others, we believe that chemotherapy-associated cognitive dysfunction is likely multifactorial and consists of variable presentation of cognitive symptoms.^{13,16} One important pathway involves psychological distress. Typically 30% to 40% of breast cancer patients experience significant distress in the form of anxiety and depression, a rate that is much higher than that found in community samples.¹⁷⁻¹⁹ Green and colleagues²⁰ reviewed a number of theoretical and empirical studies showing that people with health problems who report subjective cognitive decrements are more likely to have emotional difficulties than

Table 1. Possible Cognitive Sequelae Associated With Adjuvant Chemotherapy Regimens

<i>Specific Problem</i>	<i>Agent Responsible</i>
Problems with thinking, learning, and memory	Methotrexate, multiagent chemotherapy, bortezomib
Structural changes in the brain	Methotrexate, multiagent chemotherapy, bortezomib
Paralysis	Methotrexate, multiagent chemotherapy, bortezomib
Seizure	Methotrexate, multiagent chemotherapy, bortezomib
Numbness and tingling	Cisplatin, vinca alkaloids, taxanes, oxaliplatin

From the Institute of Medicine.^{10(p73)}

objective deficits. Specifically, in a study of 104 breast cancer patients, van Dam and colleagues³ found a significant association of psychological distress (anxiety and depression) on cognitive functioning. These previous studies provide a solid theoretical and empirical basis to argue that psychological distress, in and of itself, may induce cognitive dysfunction. Our observation is far from novel. In their preliminary report from a large-scale longitudinal study of cognitive function in women who have had surgery for early breast cancer, Shilling and colleagues²⁰ declared that “fatigue, anxiety, depression and changes in quality of life can all impact on cognitive function.”

Evidence is also mounting that systemic adjuvant therapy for early-stage breast cancer may result in cognitive impairment, irrespective of the presence or absence of psychological distress.²² Brezden and colleagues⁵ forcefully argued that their results in conjunction with 3 previous studies²⁴ strongly support the hypothesis that chemotherapy induces somatic dysfunctions and neurostructural changes that are responsible for cognitive dysfunction. Since that time, a longitudinal study by Shilling and colleagues has been published that shows that even after controlling for psychological distress, chemotherapy is directly implicated in cognitive dysfunction.²⁰ Furthermore, a forthcoming study by Silverman and colleagues²³ documents specific alterations in the activity of the frontal cortex, cerebellum, and basal ganglia in breast cancer survivors by functional neuroimaging 5 to 10 years after completion of chemotherapy.

We summarize our understanding of the above-mentioned literature with reference to proposed multifactorial etiological models of chemotherapy-associated cognitive dysfunction.^{14,21} We present a modified, simplified form (see Figure 1), which we use to call attention to the way acupuncture may be used as a potential treatment option. The progression

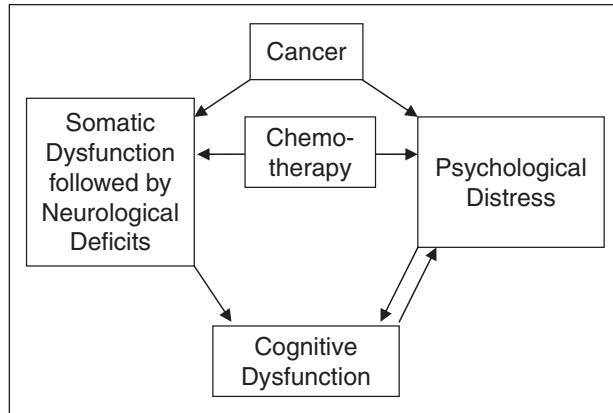


Figure 1 Model of factors contributing to objective and subjective chemotherapy-associated cognitive dysfunction.

of cancer may induce somatic dysfunctions and then structural neurological deficits, as well as psychological distress, the latter arising from anxiety and stress associated with the diagnosis and cancer itself. The primary purpose of chemotherapy is to kill tumor cells, but it also may give rise to somatic problems and structural deficits, as well as psychological distress, the latter arising from treatment-induced anxiety and stress.

Published models emphasize that both cancer and its treatment have the potential to operate along either or both objective (somatic dysfunctions and structural deficits) and subjective pathways (psychological distress) to induce cognitive dysfunction. Note that the model in Figure 1 specifically acknowledges the potential for a feedback loop between psychological distress and cognitive dysfunction, with cancer and chemotherapy giving rise to psychological distress, which then impairs cognitive functioning, which in turn leads to more psychological distress, and so forth. In the following section, we present and summarize research literature pertaining to the potential for acupuncture to alleviate chemotherapy-associated cognitive dysfunction, especially in light of the distinction between objective and subjective etiologies.

Acupuncture for Neurological Conditions

The practice of acupuncture encompasses a heterogeneous set of interventions in that a practitioner may induce a wide range of biologic responses either locally at the stimulation site and/or distally through the activation of pathways in the peripheral and central nervous systems.²⁴ Whether local or distal, needling occurs at acupuncture points, which are in the vicinity of peripheral nerves and their bifurcations, neuromuscular attachments, blood vessels, and ligaments.²⁵ Chinese medical theory posits that acupuncture is a

specific treatment modality that physicians may use to enhance the body's endogenous resistance to disease by stimulating innate self-healing mechanisms.²⁶ Meta-analyses show that acupuncture and/or electroacupuncture is an effective modality for treating a variety of medical conditions, including first-day vomiting after chemotherapy,²⁷ chronic headache,²⁸ and relief of lower back pain.²⁹ In China, acupuncture is very commonly used to treat cerebrovascular problems.³⁰ Productive efforts to assimilate acupuncture into a Western-oriented clinical practice require further theoretical development and appropriate empirical research, neither of which are trivial tasks for understanding the ways in which acupuncture may promote recovery among people with chemotherapy-associated cognitive dysfunction.

Following James Reston's description in the *New York Times* about his acupuncture treatment when in China as part of Nixon's delegation,³¹ the US media persuaded many lay people through colorful language and stunning photographs that acupuncture could be a powerful analgesic. In response to funding opportunities provided by the American government, scientists initiated research to identify a neural explanation for the effects of acupuncture.³² Ensuing primate studies and human neurophysiological studies revealed that acupuncture activates nerve fibers within muscles, which in turn send messages to the spinal cord and then activate the spinal cord, brainstem (periaqueductal gray area), and hypothalamic (arcuate) neurons.³³

In recent years, researchers have further specified specific pathways and central sites for acupuncture and electroacupuncture in the anterolateral tract in the spinal cord column, the reticulogigantocellular nucleus, the raphe magnus, the dorsal part of the periaqueductal central gray matter, the posterior and anterior hypothalamus, the medial part of the centromedian nucleus of the thalamus, and the dorsal medullar-thalamic pathways.³⁴⁻³⁸ They have also shown that needling certain acupuncture points triggers the release of neurotransmitters, neurohormones, and other central nervous system changes including opioid peptides, enkaphalins, endorphins and dynorphins, serotonin, catecholamines, and inorganic chemicals and amino acids such as glutamate and GABA.^{24,38-44} Finally, the research community has also investigated the ways in which needling of certain acupuncture points activates the hypothalamus and pituitary axis.⁴⁵⁻⁵⁰

Pioneering neuroimaging research by Cho and colleagues has led to several functional magnetic resonance imaging studies investigating a hypothesis of neurofunctional modulation of the central nervous system by acupuncture effects.⁵¹ This stream of research

has demonstrated that acupuncture elicits regionally specific, quantifiable activation of the central nervous system.^{43,51-56} Recent studies are especially pertinent to discussions of chemotherapy-associated cognitive dysfunction because they document that acupuncture stimulation is associated with activity in the human cerebellum, which is known to play a crucial role in higher-order cognitive functions.^{43,56}

Concerning the use of acupuncture to manage chemotherapy-associated cognitive dysfunction, if it arises from structural damage to the nervous system, studies on stroke and dementia provide plausible biological mechanisms. For stroke patients, Johansson and colleagues hypothesize that acupuncture may improve functional recovery after stroke by influencing brain plasticity during the functional reorganization that occurs following neuronal injury.^{57,58} Acupuncture is one example of a sensory stimulation that may favorably modify remodeling processes, in this case through positive hemodynamic and rheologic effects on the cerebral circulation.^{24,59,60} Meta-analyses, however, have not shown a cross-study effect of acupuncture in promoting motor recovery and disability, in part because those studies with positive results are rated as having a poor study design.⁶¹⁻⁶³ Similarly, studies of dementia suggest that following acupuncture, cerebral blood vessels dilate, thereby improving brain circulation, increasing oxygen supply, and increasing the ratio of glucose utilization in brain tissues.⁶⁴ Although these studies on stroke and dementia, especially combined with the aforementioned basic science studies, suggest that acupuncture may be useful for managing issues arising from structural neurological problems, at this point, advantages remain theoretical and somewhat controversial.^{24,33}

In terms of psychological distress, Cohen et al¹¹ provided a review of evidence suggesting that acupuncture may ameliorate more subjective conditions, especially depression and anxiety. A comparative study found electroacupuncture to be as effective as maprotiline in ameliorating depression (as measured by the Hamilton Depression Rating Scale and the Self-rating Scale for Depression).⁶⁵ A single-blind, placebo-controlled study showed that acupuncture, both standard and placebo, improved the course of depression more than pharmacologic treatment (mianserin) as assessed by the Global Assessment Scale, Bech-Rafaelson Melancholia Scale, Clinical Global Impressions Scale, and a self-rating scale.⁶⁶ Another comparative study on depression showed electroacupuncture to induce a better therapeutic efficacy for anxiety somatization and cognitive process than a pharmacologic treatment (amitriptyline), with fewer side effects.⁶⁷ A placebo-controlled study found auricular acupuncture to be more effective than placebo acupuncture in reducing

anxiety levels.⁶⁸ A placebo-controlled study on patients with generalized anxiety disorders found that acupuncture significantly reduced anxiety.⁶⁹ Although these studies were conducted with cancer-free patients, the promising results suggest that acupuncture may address cancer-related psychological distress.

Discussion

Chemotherapy, unfortunately, carries a “cost of survival”¹⁰ in the form of adverse side effects, of which one is cognitive dysfunction. Medical researchers are experimenting with the use of several different pharmacologic agents for preventing and ameliorating cognitive dysfunction associated with cancer treatment, including nerve growth factor, amifostine, methylphenidate, and corticosteroids.²¹ However, these treatments may result in additional side effects and sometimes interact harmfully with other prescribed medications.

Acupuncture is another possible option. It is safe in that serious events occur rarely in practice (0.05 per 10 000 acupuncture treatments), of which some, such as infection, are preventable.⁷⁰ In this article, we have reviewed relevant literature to identify plausible reasons to suggest that acupuncture could be used to therapeutically address chemotherapy-associated cognitive dysfunction. We found limited evidence that acupuncture may be used to manage structurally induced neurological and neurovascular problems and promising evidence that acupuncture can be used to alleviate psychological distress. Our preliminary position is yes, there is limited evidence that acupuncture may be used to manage neurological problems arising from somatic dysfunctions and structural deficits and promising evidence that acupuncture can be used to alleviate psychological distress.

Weiger and colleagues¹² proposed criteria for making clinical recommendations in response to patient inquiries about specific CAM modalities for cancer-related conditions. In this framework, physicians will respond to patient inquiries about usage of acupuncture with 1 of 4 different positions that range along a continuum of support from 1 = recommend; to 2 = accept, may consider recommending; to 3 = accept; to 4 = discourage. Since acupuncture is safe and our review of acupuncture for similar neurological conditions theoretically shows plausible potential benefits, we suggest that in responding to such inquiries, physicians use either the category of “accept, may consider recommending” or “accept,” the latter without any reservations or conditions.

Given that there is currently a lack of proven options for chemotherapy-associated cognitive dysfunction, we consider it very worthwhile to carefully investigate acupuncture. Our group sees prospective clinical trials as the most valuable method to further

explore the efficacy of acupuncture for ameliorating and/or alleviating cancer-related cognitive dysfunction. Indeed, one reason for conducting the review we report here is that our group has initiated a randomized controlled trial to formally investigate the hypothesis that acupuncture may improve outcomes for cancer survivors, with one specific outcome concerning alleviation of chemotherapy-induced cognitive dysfunction.

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