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COL (RET) ELSPETH CAMERON RITCHIE, MD, MPH; AND L.T. KYLE J. GRAY, MD, MA

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Directions in Psychiatry

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CME Lesson 16
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### Institute of Medicine Core Competencies:

Provide Patient-Centered Care: Identify, respect, and care about patients’ differences, values, preferences, and expressed needs; relieve pain and suffering; coordinate continuous care; listen to, clearly inform, communicate with, and educate patients; share decision-making and management; and continuously advocate disease prevention, wellness, and promotion of healthy lifestyles, including a focus on population health.

Work in Interdisciplinary Teams: Cooperate, collaborate, communicate, and integrate care in teams to ensure that care is continuous and reliable.

Employ Evidence-Based Practice: Integrate best research with clinical expertise and patient values for optimum care, and participate in learning and research activities to the extent feasible.

Apply Quality Improvement: Identify errors and hazards in care; understand and implement basic safety design principles, such as standardization and simplification; continually understand and measure quality of care in terms of structure, process, and outcomes in relation to patient and community needs; and design and test interventions to change processes and systems of care, with the objective of improving quality.

Utilize Informatics: Communicate, manage, knowledge, mitigate error, and support decision-making using information technology.

### ACGME Competencies:

Patient Care that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health.

Medical Knowledge about established and evolving biomedical, clinical, and cognate (e.g. epidemiological and social-behavioral) sciences and the application of this knowledge to patient care.

Practice-Based Learning and Improvement that involves investigation and evaluation of their own patient care, appraisal and assimilation of scientific evidence, and improvements in patient care.

Interpersonal and Communication Skills that result in effective information exchange and teaming with patients, their families, and other health professionals.

Professionalism, as manifested through a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population.

Systems-Based Practice, as manifested by actions that demonstrate an awareness of and responsiveness to the larger context and system of health care and the ability to effectively call on system resources to provide care that is of optimal value.

### ABMS Competencies:

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Part III-Assessment of Knowledge and Cognitive Expertise: They demonstrate, through formalized examination, that they have the fundamental, practice-related and practice environment-related knowledge to provide quality care in their specialty.

Part IV-Improvement in performance and practice: They are evaluated in their clinical practice according to specialty-specific standards for patient care. They are asked to demonstrate that they can assess the quality of care they provide compared to peers and national benchmarks and then apply the best evidence or consensus recommendations to improve that care using follow-up assessment.

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The objective of this continuing medical education program is to present participants with an expanded clinical skill set and raised awareness of clinically relevant issues in their profession. They will review key diagnostic criteria, cutting-edge treatment strategies, and practice points they can implement in the challenges of daily practice while providing evidence-based care to patients and clients suffering psychiatric and comorbid medical disorders. The expected outcomes include an increase in knowledge, competence, professionalism, and performance.

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This CME program was created from a learning needs assessment of participants in previous CME programs, who are virtually all physicians and other mental health clinicians. Their expressed needs were assessed by the Medical Director, the Program Advisory Board members, and editorial staff in the development of this curriculum.

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The “Three Buckets” Model for Treating Posttraumatic Stress Disorder (PTSD):
Medication, Therapy, and Everything Else

COL (ret) Elspeth Cameron Ritchie, MD, MPH; and L.T. Kyle J. Gray, MD, MA

No commercial support was used in the development of this CME lesson.
This lesson mentions the use of prazosin which is not yet approved by the Food and Drug Administration for treating PTSD.

KEY WORDS: Military • Veterans • Posttraumatic stress disorder (PTSD) • Complementary and alternative medicine (CAM) • Meditation • Animal-assisted therapy • Acupuncture • Transcranial magnetic stimulation (TMS)

LEARNING OBJECTIVES: Clinicians will be enabled to: (1) define PTSD and introduce a “three buckets” concept as an organizational framework for the variety of PTSD treatment options, (2) understand the appropriate use of selected CAM therapies and the limitations and advantages of these therapies, (3) consider the scientific basis for TMS as an emerging treatment for PTSD, and (4) identify additional resources to incorporate this technology into clinical practice.

LESSON ABSTRACT: PTSD is a complex psychiatric disorder with common comorbidities that can be difficult to treat. Conventional evidence-based therapies include trauma-focused cognitive behavioral therapy and certain antidepressants. However, these treatments may not be tolerated or preferred for many individuals for a variety of reasons, or they may only be partially effective. This lesson familiarizes the clinician with a variety of CAM treatment options for PTSD, as well as the rapidly growing use of TMS for PTSD. We review the basics of various meditation practices, animal-assisted therapy, acupuncture, and TMS and potential ways they can be incorporated into practice. The research on CAM will also be briefly discussed.

COMPETENCY AREAS: This lesson focuses on providing patient care. Healthcare providers will come away with a useful framework to approach their treatment of PTSD, with a specific focus on treatments that are not yet as evidence-based. This lesson helps providers to increase their knowledge of what these treatments are so they can have an informed and open dialogue with patients in planning their treatment.
Introduction

Posttraumatic stress disorder (PTSD) is a complex disorder that involves several cognitive, emotional, and behavioral responses to an experienced or witnessed trauma that persist longer than one month and cause dysfunction in the patient’s life. An estimated 6.8% of Americans will suffer from PTSD in their lifetime.1

While PTSD continues to gain attention in the scientific literature and media, it is important to recognize that this is not just a disorder experienced by military service members. The patients who suffer from this disorder form a heterogeneous group and, not surprisingly, there is no silver-bullet treatment. Practitioners treating this disorder are best served by having an array of treatment options. This review introduces the idea of the “three buckets” concept for PTSD treatment.2 The first two buckets comprise the two broad categories of evidence-based therapies: medication and psychotherapy. The therapies in these two buckets have proven to be effective in large, randomized controlled trials. Our review focuses specifically on the “third bucket” that comprises “everything else.” The “everything else” refers to treatments that have not yet been as rigorously tested but are nevertheless very helpful in certain individuals. This definition includes complementary and alternative medicine (CAM) and emerging treatments.

While there are many therapies within the third bucket that deserve attention, we highlight the ones that we have found most useful. These include meditation, animal-assisted therapy, acupuncture, and transcranial magnetic stimulation (TMS).

Current Definition of PTSD

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is the 2013 update to the American Psychiatric Association’s classification and diagnostic tool, which, in the United States, serves as a universal authority for psychiatric diagnosis.3 This manual describes the criteria for the diagnosis of PTSD.

DSM-5 criteria now identify the trigger to PTSD as exposure to actual or threatened death, serious injury, or sexual violation. The diagnosis of PTSD is currently based on 8 criteria from the DSM-5.

The first 4 criteria pertain to the “actual event” and must result from one or more of the following scenarios, in which the individual:

1. directly experiences the traumatic event
2. witnesses the traumatic event in person
3. learns that the traumatic event occurred to a close family member or close friend
4. experiences first-hand repeated or extreme exposure to aversive details of the traumatic event

The disturbance, regardless of its trigger, causes clinically significant distress or impairment in the individual’s social interactions, capacity to work, or other important areas of functioning. It is not the physiological result of another medical condition, medication, drugs, or alcohol.

Symptoms that accompany PTSD should be present for at least one month following the initial traumatic event and include the following: re-experiencing, avoidance, negative cognitions and mood, and arousal; more specifically:

- Re-experiencing covers spontaneous memories of the traumatic event, recurrent dreams related to it, flashbacks, or other intense or prolonged psychological distress.
- Avoidance refers to distressing memories, thoughts, feelings, or external reminders of the event.
- Negative cognitions and mood represents myriad feelings, from a persistent and distorted sense of blame of self or others, to estrangement from others or markedly diminished interest in activities, to an inability to remember key aspects of the event.
- Finally, arousal is marked by aggressive, reckless, or self-destructive behavior, sleep disturbances, hypervigilance, or related problems.
Common Comorbidities with PTSD

Trauma exposure can lead to a variety of negative mental and physical health sequelae beyond PTSD symptomatology, and as such, it is commonly associated with at least one comorbidity. In fact, according to National Comorbidity Survey data, 50% of patients with PTSD have three comorbid psychiatric diagnoses (16% and 17% have one and two additional psychiatric diagnoses, respectively). Substance use disorders, depressive disorders, and anxiety disorders appear to be the most common comorbid psychiatric conditions; the prevalence rates of these disorders are two to four times higher in patients with PTSD than those without.

Among physical conditions, perhaps the most striking evidence is for comorbid traumatic brain injury (TBI) and chronic pain. Regarding the former, among the subpopulation of American soldiers returning from Iraq and Afghanistan diagnosed with mild TBI, 62% screen positive for PTSD. This represents a nearly six-fold increase from the 11% of soldiers overall who screen positive for the disorder.

For chronic pain, studies show up to one half to three-quarters of patients with PTSD have a significant chronic pain condition. Scioli-Salter et al. provide an interesting review that offers insight into some of the shared underlying neurophysiology of the conditions and their implications for treatment. Importantly, they note that patients who have both conditions experience more pain, emotional distress, and disability than patients with either condition alone.

With this information in mind, it is key to consider a patient’s comorbidities when prescribing treatment. For example, knowing that a patient suffers from chronic pain may lead a provider to consider acupuncture over other CAM modalities, as acupuncture is often commonly used to treat pain as well.

The “Three Buckets” Concept

We have already briefly introduced the concept of our three bucket framework. To review, the first bucket is evidence-based medication options; the second bucket is evidence-based psychotherapy options; the third bucket is “everything else”—i.e., options that have not yet been evidenced in multiple large, randomized, controlled trials.

While many of the therapies in the third bucket are starting to accumulate more rigorous empirical support, most are still in the anecdotal phases of evidence accumulation. Some, such as meditation and acupuncture, have their roots established in thousands of years of tradition but little scientific theory. These have their origins in ancient Asian medicine traditions. Others in this bucket, such as TMS, are rooted in Western medicine and scientific theory but are just emerging as tested therapies for PTSD.

We encourage an open dialogue between patients and practitioners to help choose a regimen that works for them. Before delving deeper into the pros and cons of the third bucket, it is helpful to briefly review the first two and why patients may shy away from them.

Medications can be very helpful for PTSD. The first line is usually the antidepressant classes of selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs). Side effects are usually mild, such as dizziness and nausea. These usually go away in a few days.

More problematic side effects are sexual ones, which include delayed erections and decreased libido. These effects can usually be managed, for example, by switching medications, taking drug holidays, or by adding phosphodiesterase inhibitors, such as sildenafil (Viagra). However, it is important to ask about these or risk nonadherence and the patient not returning for a follow-up appointment.

Additional medication options include the alpha-blocker prazosin (Minipress), which is not yet FDA-approved for PTSD-related nightmares but is frequently used for this purpose. The main limiting factor for this medication is orthostasis. Patients should thus be educated to get up slowly from lying down.

Many practitioners prescribe second-generation antipsychotics (usually quetiapine (Seroquel) or risperidone (Risperdal) for refractory or partial response cases. The evidence for the use of these agents is not as strong as for the aforementioned medications, and they carry significant health risks in their association with metabolic syndrome (i.e., weight gain, diabetes, and hyperlipidemia). However, clinical evidence points to their utility in some cases.
The second bucket includes all trauma-focused cognitive-behavioral therapies, such as exposure therapy (including virtual reality exposure therapy) and cognitive behavioral therapy (CBT). In general, this process includes talking about the trauma and reducing the anxiety associated with it. There are two main limiting factors specific to this approach. First, patients may not be able to tolerate the increased anxiety they experience during sessions. Second, they may have an inability to establish a good therapeutic alliance.9

Understanding these limitations and the reasons our patients drop out of treatment can help us address this problem. Unfortunately, a recent study shows that only 52% of soldiers who screened positive for PTSD received minimally adequate care (four or more visits in six months), and 24% dropped out of care.9 Of those who dropped out, 39% reported not liking the medication offered and two-thirds reported some form of discomfort with the mental health professional, e.g., that the practitioner was not adequately caring, communicative, or competent.

Therefore, understanding these limitations of the first two buckets (or approaches), we endeavor to discuss how treatments from the third bucket can be incorporated into practice.

Complementary and Alternative Medicine

First, it is important to clarify terms. According to the National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH), “complementary” refers to non-mainstream practices that are used together with conventional medicine, and “alternative” medicine is the term used when a practice is used in place of conventional medicine.10 These practices are increasingly integrated into conventional medicine (prompting the use of another related term, “integrative medicine”).

CAM is commonly used by military members with PTSD (45% of active duty military versus 38% of civilians use CAM).11 The Veterans Affairs (VA) healthcare system reports that nearly 90% of their facilities offer CAM (mostly meditation), according to a 2011 survey.12 This survey was reported during a meeting held in 2011, sponsored by the VA’s Office of Research and Development. The meeting included experts from the VA, Department of Defense, and National Institutes of Health on CAM for PTSD and concluded in deciding to fund several ongoing clinical trials on meditation.13 They also conducted a review that identified seven randomized controlled trials and two nonrandomized studies of CAM for PTSD.14 They found the strongest evidence (moderate) of the benefit of acupuncture and recommended more rigorous study on this method and meditation.

Our review will focus on three areas of CAM for PTSD in which we have the most experience and for which the most evidence is available: meditation, canine therapy, and acupuncture. Many other CAM techniques are used for PTSD. A more in-depth look at these other techniques is available in the book Posttraumatic Stress Disorder and Related Diseases in Combat Veterans.15

Meditation

Meditation is the most widely used CAM for PTSD.12 It is a self-management approach that is safe, cost-friendly, portable, and easy-to-learn. The “self-management” aspect of meditation is often considered one of its greatest strengths in that it empowers patients to take an active role in their own healing process and gives them a sense of control over their symptoms.

Meditation can be broadly conceptualized as a form of “mental training.” It has a long history rooted in ancient cultures and has evolved to take numerous styles. Most research on meditation for PTSD focuses on three broad types: mindfulness meditation (MM), mantra meditation, and compassion meditation.16

MM has been the most well-studied type of meditation and has additional evidence that it may be useful in patients with comorbid conditions such as depression, substance use disorders, sleep disturbances, and chronic pain.16 Thus, it may be preferred in patients with these comorbidities. However, the best choice for the patient will largely depend on which practice most resonates with him or her (and to which they most likely will adhere), availability, and the teacher’s experience.

Regardless of the type of meditation, there is evidence of the activation of a common cognitive pathway wherein the benefits of meditation for PTSD may be derived. A recent quantitative meta-analysis of 10 functional neuroimaging studies across many different meditative practices showed the activation of the
The significance of these findings is still being determined, we know that many of the symptoms of PTSD, such as hyperarousal and persistent fear states, correlate with an overactivation of the amygdala and that activation of the prefrontal cortex can help regulate this response, leading to greater stress tolerance and self-acceptance.18, 19

**Mindfulness Meditation:**

MM has a primary focus on breathing with the aim of achieving open, nonjudgmental awareness and acceptance. Research findings consistently demonstrate that this form of meditation produces improved health-related quality of life and well-being as well as reduced avoidance, depression, and numbing symptoms. Furthermore, there is some evidence that it has beneficial effects on other conditions such as hypertension and substance use disorders.20

**Mantra Meditation:**

Mantra meditations are a group of meditations that include mantra repetition, transcendental meditation (TM), and relaxation response training that use the common technique of repeating a word, phrase, or sound. This process aims to redirect the person’s attention from rumination and maladaptive thought patterns, instead creating a sense of peace and relaxation.21, 22 Similar to MM, mantra meditations have been shown to reduce the symptoms of PTSD.23, 24 This reduction in symptoms is thought to be mediated through a physiologic relaxation response.23, 25

Mantra repetition, specifically, has been associated with an increase in existential spiritual well-being that may contribute to its overall health and mental health benefits. Researchers cite the importance of the spiritual meaning of the words selected by the individual and their potential power in eliciting feelings of well-being and self-confidence.24, 26

**Compassion Meditation:**

Compassion meditation emphasizes a sense of “loving-kindness” to all beings. It takes many forms, but it is primarily informed by Buddhist practice. Tonglen is one specific type of compassion meditation that is based on the Tibetan Buddhist tradition and involves the visualization of transforming another person’s suffering into compassion.27

Several studies suggest that compassion meditation has several positive outcomes that would benefit patients with PTSD. Like other meditative forms, compassion meditation has been shown to reduce hyperarousal. It additionally increases social connectedness, which can translate into improved social support and personal relationships, which are key to recovery. Finally, compassion meditation has been shown generally to both increase positive emotions and reduce negative effects, which may, among other obvious benefits, improve the patient’s capacity for resilience, making a case not just for its use in recovery but also in the prevention of PTSD.15, 26, 28–32

**Animal-Assisted Activities and Therapy**

Two of the main categories of incorporating animals into health care are animal-assisted activities, most commonly in the form of service dogs, and animal-assisted therapy.

**Animal-Assisted Activities:**

The *Americans with Disabilities Act* (ADA) defines “service animals” as animals that have been individually trained to do work or perform tasks to aid a person with a disability.33 The ADA specifically identifies calming a person with PTSD as one such specific task, but it is important to distinguish these kinds of highly trained dogs from pets whose sole function is to provide emotional support. The service dog designation allows for the dog to accompany the person with PTSD in all areas of facilities where the public is normally allowed to go. Service dogs of veterans may be qualified to receive veterinary care benefits through the VA, and we recommend checking with your local branch.

**Animal-Assisted Therapy:**

Scientific evidence demonstrating improvements in symptoms of PTSD as a result of canine and equine therapy lags behind the remarkable growing interest and popularity of these programs. However, a growing body of evidence shows that the nurturing involved in this type of therapy provides positive sensory stimulation that can activate the anti-stress and pro-social neural and neurohormonal networks (e.g., increase oxytocin) in both humans and animals.34–38 Furthermore, interactions with animals have been shown to lower blood pressure and have a calming effect on individuals with dissociative disorder.39, 40
The mere presence of animals in a healthcare setting may even be therapeutic. Studies have shown that their presence can increase individuals’ willingness to enter into therapy, facilitate the therapeutic alliance, reduce the rate of attrition, and reduce symptoms of trauma.41–43 One recent study found that adults who wrote about a recalled trauma in the presence of dogs found the exercise less distressing and had significantly fewer symptoms of depression at follow-up than those who completed the writing exercise without a dog.33

Animal-assisted activities and therapy can be challenging to incorporate into practice; we recommend looking thoroughly into local resources, ensuring the program is reputable and will fit your patient’s needs. When done correctly, this type of therapy appears to be particularly beneficial to patients who struggle with more of the avoidance and isolation symptoms of PTSD; the animals can help serve as a bridge to broader, healthier social interactions.

**Figure 1:**
Photograph from National Intrepid Center of Excellence (NICoE) Facebook page.

Photo available online: https://www.facebook.com/NationalIntrepidCenterofExcellence/photos/a.10150163476202035.299199.156392117034/10153289164492035/?type=3 &theater

Acupuncture

Acupuncture is an ancient treatment that utilizes thin, filament-like needles placed on the body to treat a variety of health (and even spiritual) problems. Its foundation is in traditional Chinese medicine (TCM), but since its first use thousands of years ago, it has been adopted by cultures all over the world, leading to a multitude of different practice styles and philosophies. However, the core aspects of the treatment remain the same.

Acupuncture was originally developed around a concept of a circulating life force known as *qi*. This concept has elicited a great deal of skepticism and controversy and is not adopted as a framework by all practitioners. However, it is useful to note at least for historical reference.

*Qi* is thought to be conducted between the surface of the body and internal organs via 12 main and 8 secondary pathways called meridians. The concept suggests that the normal flow of *qi* can be disrupted by the opposing forces of yin and yang, influenced by environmental factors such as illness, trauma, and stress. Acupuncture targets points along the meridians in an effort to balance yin and yang and restore the normal flow of *qi*.46

Modern scientists, who may or may not subscribe to the above theory, have attempted to explain some of the perceived benefits of acupuncture through other means. However, the clinical application of modern research on acupuncture is often limited by the study design, sample size, the selection of appropriate controls, and the non-standardized selection of points based on traditional methods of diagnosis and treatment.47

While the specifics of this nascent research go beyond the scope of this review, some of the research is starting to point to possible mechanisms such as the release of endogenous opioids; the modulation of neurotransmitters, such as serotonin, norepinephrine, dopamine, and GABA; effects on neurotrophins and cytokines to reduce inflammation; effects on the autonomic nervous system; and the regulation of the neuroendocrine system.48–50 Each of these factors is known to be dysregulated to some degree in patients with PTSD.

*In regards to how acupuncture fares against conventional treatments for PTSD (or waitlist controls), the evidence is again mixed but seems generally favorable.* A systematic review of four randomized controlled trials (RCTs) and two uncontrolled trials were reviewed and had several important findings. One high-quality RCT showed significant improvements (i.e., on a self-report posttraumatic symptom scale and three other outcome measures) compared to waitlist controls, but not significantly greater than the improvements seen with CBT. Two lesser-quality studies, one of which had a high risk of bias, showed that acupuncture plus
moxibustion (another TCM technique) was superior to oral SSRI therapy for PTSD.51

As with all CAM, we emphasize the need for more large, RCTs before acupuncture can be considered as a first-line treatment. The extant literature is encouraging, however, and acupuncture remains an excellent choice for adjunctive therapy for PTSD, particularly in patients with comorbid chronic pain.

Transcranial Magnetic Stimulation (TMS)

TMS is a noninvasive brain stimulation technique that is FDA-approved for the treatment of depression in patients who do not respond to at least one antidepressant in their current episode. Given its efficacy in the treatment of depression and its promise as a more benign, localized brain stimulation therapy alternative to ECT, it continues to be vigorously researched and used off-label for a variety of additional uses.

Without going into technicalities that are beyond the scope of this review, TMS devices use a coil placed near the patient’s scalp to generate an electromagnetic current. This current stimulates a change in flow of the ionic current of the electrically conductive neuronal tissue, leading to neurotransmitter release. This local stimulation in turn can have downstream effects on additional neural networks, leading to broader effects—these effects will vary depending on the region targeted.52

Rossi et al have successfully used TMS as a diagnostic technique to measure brain GABAergic and glutamatergic tone. Using a paired pulse technique, they reported in 2009 that 20 drug-naïve patients with PTSD had reduced GABAergic tone in the bilateral hemispheres and increased glutamatergic tone in the right hemisphere.53 Animal models have also demonstrated reduced GABA levels in the setting of chronic unpredictable mild stress and that TMS reversed these neurochemical changes.54 These findings together suggest the stimulation of the left dorsolateral prefrontal cortex (DLPFC) and inhibition of the right DLPFC as a potential pulse sequence model for PTSD.55,56

Currently, two manufacturers license TMS machines for use for major depression: MagVenture (the MagVita system) and Neuronetics (the Neurostar system). They offer training for practitioners considering incorporating this therapy into their practice. Treatment for depression typically involves treatment 5 times a week for 4–6 weeks; research is ongoing to determine whether similar durations are necessary for PTSD and other conditions.

Others

The foregoing is not an exhaustive list of CAM or emerging therapies for PTSD. Additional treatment modalities include:

- Yoga
- Exercise therapy
- Art therapy
- Emerging psychotherapies such as Accelerated Resolution Therapy (ART)57
- Cranial electrotherapy stimulation ([CES] e.g., alpha-stimulation technology)58
- Stellate ganglion block59

These therapies are wide-ranging; some of them require robust training by the practitioner (e.g., ART), some can be costly (e.g., CES), and others are low to no cost and are generally recommended by physicians to treat and prevent any health conditions (e.g., exercise). Thus, we almost always recommend exercise to all patients, unless there is some physical contraindication,
particularly given its demonstrated beneficial effects in many psychological conditions, including PTSD.\textsuperscript{60–62}

**Conclusion**

PTSD is a complex disease that can be difficult to treat. There are numerous barriers to adequate care, including limitations to the more established, evidence-based treatments. Providing additional options as adjuncts or alternatives can increase the likelihood of successful treatment. We encourage providers to work with patients to determine what is effective for them. We cannot yet predict which treatment modality works best for any one individual, although individual patient factors, such as comorbidities and predominant symptoms, can help guide treatment choices. The discussion among patients and providers should include what treatments are most accessible and affordable for the patient, and providers should be familiar with local resources that offer these services.

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**About the Faculty**

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**Kyle J. Gray, MD MA:** Dr. Gray is a resident at Walter Reed National Military Medical Center in the National Capital Consortium Psychiatry Program.
References


Multiple-Choice Questions

61. Which of the following criteria are necessary to diagnose PTSD?
   A. Hallucinations
   B. Hyperarousal
   C. Disorganized behavior
   D. Somatic symptoms

62. The “three buckets” concept for PTSD refers to:
   A. a broad framework for the major categories of treatment modalities.
   B. three broad patient archetypes based on symptom clusters.
   C. complementary, alternative, and emerging treatments (CAM) for PTSD.
   D. three main pharmacotherapies for PTSD (SSRIs, prazosin, atypical antipsychotics).

63. Which brain region, which is also a target region for TMS, does meditation appear to activate?
   A. Hippocampus
   B. Frontal cortex
   C. Amygdala
   D. Prefrontal cortex

64. According to the lesson, which of the following is generally recommended to every patient?
   A. Fish oils
   B. Meditation
   C. More exercise
   D. Prazosin
The “Three Buckets” Model for Treating Posttraumatic Stress Disorder (PTSD): Medication, Therapy, and Everything Else
By COL (ret) Elspeth Cameron Ritchie, MD, MPH; and L. T. Kyle J. Gray, MD, MA
ID#: L003379

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview
PTSD is a complex psychiatric disorder with common comorbidities that can be difficult to treat. Conventional evidence-based therapies include trauma-focused cognitive behavioral therapy and certain antidepressants. However, these treatments may not be tolerated or preferred for many individuals for a variety of reasons, or they may only be partially effective. This lesson familiarizes the clinician with a variety of CAM treatment options for PTSD as well as the rapidly growing use of TMS for PTSD. The authors review the basics of various meditation practices, animal-assisted therapy, acupuncture, and TMS and potential ways they can be incorporated into practice. The research on CAM is also be briefly discussed.

Key Point 1: “Three Buckets Model”
There are three main categories of treatment modalities for PTSD treatment, which we term the “three buckets model.”

Key Point 2: Complementary, Alternative, and Emerging Treatments (CAM)
By definition, CAM and other emerging treatments lack the quality of evidence as the first two buckets of evidence-based therapies but have unique advantages; we recommend discussing each of the three buckets with patients.

Key Point 3: Neurobiology in PTSD
Evidence from meditation studies and TMS studies implicate the importance of the prefrontal cortex in mediating an overactive amygdala in patients with PTSD.

Key Point 4: Role of Exercise in PTSD
Regular exercise may also alleviate symptoms of PTSD, and because of its overall beneficial health effects, we recommend it to all patients.
Chronic Pain, Cognitive Deficits, and Depression

Karen M. von Deneen, DVM, PhD; Jixin Liu, PhD; Jie Tian, PhD; and Yi Zhang, PhD

No commercial support was used in the development of this CME lesson.

KEY WORDS: Chronic pain • Cognitive deficits • Depression

LEARNING OBJECTIVES: This lesson will enable clinicians to (1) define chronic pain and understand its causes, (2) identify various cognitive deficits associated with chronic pain, (3) discuss possible treatment and proactive interventions for chronic pain and cognitive defects, and (4) depict how depression is diagnosed and treated in chronic pain patients.

LESSON ABSTRACT: Individuals suffering from chronic pain can have impaired higher-level cognitive skills, including executive function impairment and depression. Most clinics do not properly assess the extent to which these conditions affect patients’ daily lives. Many neuroimaging studies have shown that alterations in the gray and white brain matter cause cognitive dysfunction, which presents itself in chronic pain. Therefore, it is critical to devise individualized treatment for chronic pain sufferers after a battery of neuropsychological tests.

COMPETENCY AREAS: This lesson addresses the gap in knowledge in the areas of patient care and practice-based learning and how to improve the treatment of patients with chronic pain and related complications, such as cognitive deficits and depression. Upon the conclusion of reading this lesson, readers will have a better understanding of chronic pain conditions and how to assess and manage issues associated with cognitive deficits/depression.
Introduction

Chronic pain (CP) is a condition lasting longer than 6 months and is defined as “a state of continuous learning, which has a close connection with an unconditionally pain-related stimulus, without the opportunity to disrupt the association with continuous pain” (Apkarian et al).\(^1\) It includes fibromyalgia (FMS), osteoarthritis (OA), migraine,\(^2\) chronic lower-back pain, whiplash-associated disorders (WAD),\(^3\) etc. As depicted in Figures 1 and 2, this results in functional alterations in the brain that affect various neural circuits, such as working memory, response inhibition, mental planning, mental flexibility, and emotion/behavior monitoring.\(^4, 5\) As brain function continuously reorganizes during chronic pain, new learning may be associated with the altered pattern of functional connections between brain regions.\(^2\) CP causes physical and emotional stress in both patients and their loved ones, including increased healthcare costs.\(^6\)

Figure 1: Negative Effects of Chronic Pain on Emotion and Cognition

Pain can have a negative effect on the emotions and cognitive function. Conversely, a negative emotional state can lead to increased pain, whereas a positive emotional state can reduce pain. Similarly, cognitive states such as attention and memory can either increase or decrease pain. Of course, emotions and cognition can also reciprocally interact. The minus sign refers to a negative effect and the plus sign refers to a positive effect (used with permission).\(^7\)

Prevalence, Etiology, and History of Chronic Pain, Cognitive Deficits, and Depression

Understanding the prevalence, etiology, history, and mechanisms of CP and its sequelae is crucial for diagnostic purposes and treatment in routine clinical practice and clinical trials. The prevalence of CP ranges from 7-40%, mainly being seen in women ages 45-65.\(^7\) Approximately 50% of CP sufferers complain of cognitive deficits\(^8\) and perform poorly on cognitive function tests.\(^9\) One study provided a comprehensive overview of cognitive deficits found in CP cases. There are two theories to explain what causes CP. The first is known as the limited resources theory, which states that the brain’s processing of pain stimuli disrupts other cognitive processes.\(^10\) The second theory is called maladaptive plasticity, which holds that nociceptive signals lead to alterations in the central nervous system’s structure and neurochemistry,\(^11, 12\) leading to an overly active amygdala (AMY) and a deactivated prefrontal cortex (PFC).\(^13\) An intact AMY-PFC pathway is crucial to cognitive and decision-making activities.\(^14\) Some interesting findings related to CP have been that neurocognitive defects are correlated with age; CP may cause the early onset of aging, and CP results in decreased neurocognition as age increases\(^15, 16\). Overall, the exact mechanism behind CP and the related cognitive defects is not completely understood nor is how the secondary effects of CP, including depression, anxiety, and insomnia, evolve. It is known that depression and anxiety negatively affect cognition.\(^17\) Approximately 40-50% of CP patients suffer from depression, and 20% of those score abnormally on neurocognitive tests.\(^18\) CP and psychiatric disorders share neural pathways\(^19\) and directly affect one another;\(^20\) hence, together they pose a greater danger than they do by themselves.\(^21\) Certain studies suggest that altered moods result in cognitive impairments in many CP cases.\(^22, 23\) In 2009, one group of researchers found decreased gray matter density in patients suffering from CP and depression; thus, neurocognitive defects were attributed to both.\(^24\)

Assessment and Diagnosis of Chronic Pain, Cognitive Deficits, and Depression

Neuropsychological assessments and executive function evaluations are not routinely assessed in pain management clinics because there is no easily administered gold-standard battery of tests for CP. Most importantly, executive function deficits can be difficult to assess using only paper tests and cannot fully evaluate daily life situations.\(^17, 25\) Some assessment tools used in CP are best described by Ojeda et al (2015).\(^26\) One such comprehensive test, called BRIEF-A, can
assess multiple executive function defects seen in various conditions, including CP. Other specific types of neurocognition and tests that measure them are as follows: attention and information-processing speed (the Symbol Digit Modalities Test and Trail-Making Test); working memory (the Paced Auditory Serial Addition Test or Spatial Span); memory (the Rey Auditory Verbal Learning Test and Rey Complex Figure Test); and executive functions (the Wisconsin Card Sorting Test for mental flexibility, the Stroop test for cognitive inhibition, and the Controlled Oral Word Association Test for verbal fluency) [see ref. 30 for details regarding each test].

**Figure 2:**
Psychological Processes and Behavioral Consequences Involved In Chronic Pain

Following pain (a sensory or emotional experience to an actual trauma or perceived bodily threat), a number of psychological processes, including those listed here, are involved in the response. These change processes may be resilient or resistant to the inciting events or become altered, as noted in examples of behavioral consequences. Additionally, alterations in one system may have consequences for another. The understanding of how these systems interact and can be targeted will have significant implications for treatment approaches (used with permission). 5

**Treatments and Treatment Issues**

Following the diagnosis and assessment of CP, the next step is educating the patient, on an individual basis, about how to manage and cope with his or her condition, cognitive deficits, and depression. Then, he or she can be given coping strategies with which to reduce functional disability, such as internal memorization techniques and external memory cues. Some specific examples include the following: for processing speed, Time Pressure Management is a strategy-based system for living with reduced processing speed that was originally developed for patients with concussions or brain injuries; for attention difficulties leading to inattentiveness and forgetfulness, the patient may be encouraged to set alarms or smartphone notifications as reminders of particular tasks; working memory strategies include mental or out-loud rehearsal of information; and, for executive function difficulties, such as problems with planning and organization, creating a weekly planner and learning to follow a procedure that is broken down into logical parts are helpful. For more strategy suggestions, see [http://www.latrobe.edu.au/data/assets/pdf_file/0008/256922/focusing_attention.pdf](http://www.latrobe.edu.au/data/assets/pdf_file/0008/256922/focusing_attention.pdf). The predominant reason for implementing these strategies is that they aid in neuroplasticity. Thus, a restorative approach includes repeated practice using standardized tasks that target specific cognitive domains. One such method is computerized cognitive training (CCT), which includes game-like formats (CogMed, Lumosity, CogniFit, Posit Science, and SBTPro) intended to promote neural repair. Other recommendations include reading, card games, crosswords, or puzzles as well as learning new hobbies that are socially/physically interactive.

Drug therapy can also be combined with the above-mentioned methods for better results in managing pain as well as cognitive deficits and depression. Agents such as anticholinesterases (for dementia), opioids (these cause neuroplastic alterations and should be used with caution long-term), benzodiazepines (chronic impairment of cognition), tricyclic antidepressants (memory and psychomotor speed impairments), selective serotonin uptake inhibitors (minimal effects on cognition), anticonvulsants (treat neuropathic pain well), and over-the-counter analgesics (mild effect on cognitive processes) have been prescribed for CP and/or depression, but their side effects and further cognitive impairments must be discussed with each individual patient. Alternative medicine or holistic approaches, including Traditional Chinese Medicine/acupuncture, have also been proven useful and lack many drug-related side effects.
Cognitive-behavioral therapy (CBT) is a psychological therapy program for reducing depression and anxiety in CP patients. This form of treatment involves relaxation and mindfulness techniques, managing stress, and muscle deconditioning to reduce pain.

Physical exercise has been proven to not only alleviate pain and depression but to also enhance cognition. The critical step is convincing the patient of the benefits of non-strenuous exercise, such as yoga, tai chi, swimming, walking, etc. These forms of exercise have neuroprotective effects and decrease anxiety, but more research must be done in pain populations.

Transcranial magnetic stimulation and direct current stimulation via electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) neurofeedback have also been shown to be effective methods of treating CP, cognitive deficits, and depression. These stimulate the brain regions involved in the neural pain modulatory system and cognitive networks to relieve CP, improve working memory, and regulate emotion. Finally, to view all of the methods described in this section, please refer to Figure 3.

Figure 3:
Psychological Treatments and Functions for Chronic Pain Across Brain Systems

A network of brain systems underlies alterations in psychological function in the chronic pain state. This figure shows specific psychological treatments that target alterations in psychological function across brain systems (used with permission).
Summary and Conclusions

Addressing the relationships between CP, cognitive deficits, and depression is a real issue in pain management clinics and deserves further study. Thus far, no researcher has devised an experiment regarding the training of cognitive skills in CP with endogenous pain and mood control. Preventative interventions for CP and its effects must be systematically evaluated from the onset of injury, before they become chronic. The most important question remains whether clinical focus should be on decreasing the psychological aspects of CP first, directly targeting CP, or using a graded approach. Based on the research presented, it seems that the methods that produce the best results involve a combination of therapies and approaches in dealing with CP, cognitive deficits, and depression that is tailored to the patient’s individual medical profile, needs, and goals.

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Multiple-Choice Questions

65. What is the major cause of chronic pain?
   A. Disregulated neural networks
   B. Elevated mood states
   C. Eating spicy food
   D. Living in a humid environment

66. Which one of the following is not a cognitive deficit associated with chronic pain?
   A. Decreased memory-related processes
   B. Increased pain
   C. Decreased motivation
   D. Anhedonia

67. According to the lesson, what is the best method of treating chronic pain?
   A. Physical exercise
   B. Cognitive-behavioral therapy
   C. A multifactorial approach/combination of therapies
   D. Drug treatment

68. How do clinicians diagnose depression associated with chronic pain?
   A. EEG
   B. CT
   C. MRI
   D. Neuropsychological assessment
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Best Practices in CME

Chronic Pain, Cognitive Deficits, and Depression
By Karen M. von Deneen, DVM, PhD; Jixin Liu, PhD; Jie Tian, PhD; and Yi Zhang, PhD

ID#: L003380

This valuable take-home reference translates the evidence-based, continuing medical education research, and theory acquired from reading the associated CME lesson into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The information in this lesson will be helpful to medical students, general practitioners, researchers, and family physicians, who may not have up-to-date knowledge about chronic pain and its medical consequences. Knowing the signs, symptoms, and sequelae of chronic pain can aid in prompt identification and treatment.

Key Point 1: Identification of Chronic Pain and its Consequences
The key to treating chronic pain is proactively identifying the symptoms at an early stage, before they progress to more severe pain, cognitive defects, and depression.

Key Point 2: Intervention
Immediate intervention that includes multifactorial approaches, such as cognitive behavioral therapy, pain/depression medications, and holistic approaches, prevents chronic pain conditions from progressing.

Key Point 3: Competent Staff
Seeking proper personnel and well-trained staff is important in the successful treatment of chronic pain and its sequelae.

Key Point 4: Continuing Education
Reading current research on chronic pain is important in preparing for its treatment and possible prevention. This includes working in interdisciplinary teams at university hospitals or research facilities dedicated to studying various types of strokes and providing current intervention methods.

Key Point 5: Research and Development
Being involved in chronic pain studies will help the scientific and medical community deal with chronic pain directly.
Biomarkers in Alzheimer’s Disease

Carla Bejjani, MD; Raja Mehanna, MD; and Asim Shah, MD

No commercial support was used in the development of this CME lesson.

**KEY WORDS:** Alzheimer’s disease • Biomarkers • PET scan • Aβ42 • Tau

**LEARNING OBJECTIVES:** This lesson will enable clinicians to: (1) understand the current hypothesis for Alzheimer’s disease (AD) pathogenesis, called the amyloid cascade, (2) discuss the need for and the availability and clinical utility of biomarkers of AD, and (3) discuss different imaging strategies for AD and its findings.

**LESSON ABSTRACT:** AD is pathologically defined by the accumulation of extracellular aggregates of amyloid β sheets (Aβ) and intracellular neurofibrillary tangles, dystrophic neurites, and neuropil threads of tau protein. The current diagnosis of AD relies solely on clinical criteria. The failure of many phase III studies revealed a strong need for biomarkers of AD to improve the specificity of the diagnosis, thus ensuring that non-AD demented patients are excluded from AD trials, but also to allow an earlier diagnosis and attempt a disease-modifying treatment earlier in the pathological process to ensure a higher likelihood of success. In this lesson, we review the available imaging and biological markers of AD.

**COMPETENCY AREAS:** This lesson addresses the gap in knowledge and role of biomarkers in AD. The authors utilize informatics to improve the specificity of the diagnosis of Alzheimer’s disease, which aids in early detection and treatment by the use of imaging and biological markers of AD.
Introduction

A progressive neurodegenerative disorder, Alzheimer’s disease (AD) accounts for approximately 50%–60% of all cases of dementia. Its incidence increases with age, and, with the increasing aging of populations and life expectancy, the prevalence of AD continues to rise worldwide.

AD is pathologically defined by the accumulation of two types of proteins in the brain: (i) amyloid β sheets (Aβ), forming extracellular aggregates in the form of plaques and cerebrovascular amyloid angiopathy (CAA); and (ii) tau protein, which forms intracellular neurofibrillary tangles, dystrophic neurites, and neuropil threads.

Aβ is produced by two enzymes’ sequential cleavage of amyloid precursor protein (APP). The prevailing current hypothesis for AD pathogenesis, called the amyloid cascade, suggests that Aβ aggregation is the initiating event in which the different stages of aggregates, from soluble oligomers to insoluble fibrils in plaques, impair synaptic function and ultimately damage neurons, resulting in chronic neurodegeneration, leading to cognitive impairment and finally dementia.

An extensive number of large phase III clinical trials on Aβ targeting drugs have reported no beneficial effects on cognitive symptoms in patients with sporadic AD. One explanation is that the trials enrolled patients with AD and dementia, who are thus at too advanced of a stage of the disease to benefit from this type of drug. Clinical dementia is associated with severe neuronal and synaptic loss and a heavy tangle load that are not likely to benefit from arresting Aβ aggregation or plaque removal. This underlines the need for biomarkers allowing for the detection of subjects with AD pathology before clinical dementia (necessary for the clinical diagnosis) develops. In addition, AD clinical criteria are not specific enough, with AD trials ultimately enrolling only 80% of patients with genuine AD pathology, creating yet another need for biomarkers to improve the specificity of the diagnosis.

The National Institutes of Health (NIH) defines a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” In 1998, the Ronald and Nancy Reagan Research Institute of the Alzheimer’s Association and the National Institute of Aging Working Group stated that an ideal AD diagnostic biomarker should be able to detect a fundamental feature of Alzheimer’s neuropathology, validated in neuropathologically confirmed AD cases, precise (able to detect AD early in its course and distinguish it from other dementias), reliable, simple to perform, non-invasive, and inexpensive.

Biomarkers for AD are, in fact, being developed and include the use of imaging techniques and measurements of the levels of proteins in the blood and the cerebrospinal fluid (CSF).

In this lesson, readers will review the current AD biomarker candidates, determine which ones are the most powerful, and understand the current research and clinical applications.

We will start by reviewing neuroimaging technologies as they provide a noninvasive or minimally invasive method for early AD detection.

Neuroimaging

AD is associated with progressive atrophy, synaptic dysfunction, as well as Aβ and Tau deposition. Structural magnetic resonance imaging (MRI) offers a volumetric measurements of the progressive atrophy from neuronal loss, information that can be valuable when assessing prognosis; synaptic dysfunction can be gauged with techniques measuring the fMRI blood-oxygen-level-dependent (BOLD) signal, regional metabolism with 18F-2-deoxy-2-fluoro-D-glucose (18F-FDG), and regional perfusion with 15O-water PET or single photon computed tomography (SPECT). Aβ deposition in the brain is measured with several compounds, of which (11)C-labelled Pittsburgh Compound-B (11C-PIB) has been applied to the largest number of patients. Much less experience exists with specific tau markers, of which 18F-AV-1415 is the first reported, originally as 18F-T807. 18F-FDG, amyloid, and tau studies are carried out using positron emission tomography (PET). Because metabolism and brain perfusion are coupled in AD, perfusion studies with SPECT provide information similar to 18F-FDG PET. Although SPECT brain perfusion studies are easier to perform and less expensive than PET studies, they have less spatial resolution, and thus less sensitivity and specificity, particularly at early stages of the disease.

We will now look at each of the aforementioned techniques in more detail.
MRI:
Structural MRI creates a three-dimensional image that evaluates the brain's physical structure. Serial MRIs performed in presymptomatic individuals have suggested that atrophy in some regions, particularly the precuneus and medial temporal areas, may start as early as four years of age, before the onset of cognitive impairment. In cognitively normal elderly individuals, cortical thinning in precuneus and medial temporal regions has been found to correlate with subsequent cognitive decline as much as a decade later or with amyloid deposition and reduced CSF Aβ. The pattern of cortical thinning in people who will develop AD differs from that associated with the cognitive loss from healthy aging. Regional atrophy correlates with regional Aβ deposition, particularly in the posterior cingulate cortex, in presymptomatic people or those with subjective cognitive complaints, but not in Mild Cognitive Impairment (MCI) or AD, suggesting that the damaging effect of Aβ occurs in the presymptomatic or very mildly symptomatic stages, when Aβ-reducing therapies should be applied.

In patients with MCI, thinning of the temporal cortex and precuneus is a predictor of worsening AD, particularly when combined with neuropsychological, PET, and CSF markers. Although atrophy can be appreciated visually, automated methods are more precise and facilitate longitudinal follow-up. In one longitudinal clinical study, these methods had 67% sensitivity and 69% specificity to separate stable MCI from MCI worsening to AD, 86% and 82% to separate healthy controls from MCI worsening to AD, and 93% sensitivity and 85% specificity to separate healthy controls from AD. In another longitudinal study with a 3-year follow-up, the combination of greater learning impairment and increased medial temporal atrophy was associated with the highest risk: 85% of patients with both risk factors converted to AD within 3 years, vs 5% of those with neither.

Functional MRI:
Impaired synaptic function across the various AD stages can be gauged with techniques measuring the fMRI BOLD signal, regional metabolism, and regional perfusion. Findings are concordant, but each technique is amenable to different applications. Metabolism has been studied most extensively, but the most recent developments are the increasing use of resting state BOLD fMRI to assess functional connectivity changes and of arterial spin labeling (ASL) to measure regional perfusion using non-invasive MRI.

18F-FDG PET Scan:
Regional cerebral metabolism studies with PET have used 18F-FDG as a metabolic marker. The most typical pattern found in early AD is decreased metabolism bilaterally in the parieto-temporal association cortex and posterior cingulate gyrus. Metabolism reflects synaptic activity and therefore is most affected early in the regions to which medial temporal neurons project, and may reflect impaired connectivity even in presymptomatic subjects. As atrophy corresponds to neuronal loss, it is not surprising that the regions that appear most affected on volumetric MRI and metabolic PET do not coincide early in the disease, but they partially overlap as the disease progresses. As the disease progresses, some areas of the frontal association cortex become hypometabolic, while the paracentral cortex (primary motor-sensory areas) remains preserved. The specificity and sensitivity of these findings continue to be debated. In studies with neuropathological confirmation, the sensitivity (84%–95%) has been higher than the specificity (71%–74%); that is, a normal study is seldom associated with AD. Among persons with MCI, those most likely to progress to AD have metabolic findings similar to AD. 18F-FDG PET may predict the worsening from MCI to AD better than structural MRI or SPECT.

Perfusion SPECT Scan:
The most commonly used tracers for studying cerebral perfusion with SPECT are Tc-99m hexamethyl propylene amine oxide (HMPAO, Ceretec™), a lipid soluble macrocyclic amine, and Tc-99m ethyl cysteinate dimer (ECD, Neurolite™). The pattern of decreased regional perfusion in the parieto-temporal cortex, hippocampus, anterior and posterior cingulum, and dorsomedial and anterior nucleus of the thalamus had a sensitivity of 86% and a specificity of 80% comparing AD to normal controls. In a group of 70 patients with dementia and 14 controls, all with autopsy, SPECT was most useful when the clinical diagnosis was of possible AD, with a probability of a diagnosis of AD of 67% without SPECT,
of 84% with a positive SPECT, and of 52% with a negative SPECT. However, to predict the progression from MCI to AD, SPECT has been reported to have 41.9% sensitivity and 82.3% specificity, although a meta-analysis assigned to SPECT a similar predictive value as MRI measurements. A head-to-head comparison of perfusion SPECT with metabolism PET has shown that PET has much better sensitivity and specificity than SPECT in predicting AD.

Aβ Imaging:

Brain Aβ has been imaged most extensively with “Pittsburgh Compound B” (11C-PiB), helping separate the dementias with marked Aβ deposition from the rest. Patients with AD dementia have a 50%–70% increased retention (range 20%–80%) in global cortical 11C-PiB compared with cognitively normal older individuals. PiB is only available bound to 11C, a positron-emitting isotope with a half-life of 20.4 minutes, but since 2012 Aβ-imaging compounds have been bound to 18F, with a half-life of 109.8 min. The longer half-life allows for the radiotracer to be synthesized at a facility with a cyclotron and then shipped to institutions with PET cameras, a process much less expensive than having an on-site cyclotron. These PET ligands include 18F-flutemetamol (Vizamyl), also called 3F-PiB or GE-067, 18F-florbetapir (Amyvid), also called AV-45, 18F-NAV4694, formerly known as AZD4694, and 18F-florbetaben (Neuraseq), also called AV-1. Using these amyloid tracers, a 40%–70% increase in cortical ligand retention is found, but some show lower cortical binding in patients with AD than 11C-PiB, while others have higher nonspecific white matter binding than 11C-PiB. All these tracers are approved by the FDA for use in clinical settings.

It is worth noting that PiB and the 18F PET amyloid ligands were developed to bind to aggregated Aβ with a preference for compact plaques and vascular deposits (CAA), while diffuse plaques are less prominently labeled and amorphous plaques comprising loosely aggregated Aβ containing little β-sheet structure do not bind PiB. In early AD, 11C-PiB binds mainly to the fronto-parieto-temporal association cortex, sparing the paracentral regions and primary sensory cortex. It also binds to the striatum. The regional retention of PiB-like compounds reflects the regional density of Aβ plaques. A positive amyloid PET scan is reported in 85%–90% of clinically diagnosed cases with AD dementia. Approximately 90% of PiB-positive MCI cases progress to AD dementia during clinical follow-up, while most PiB-negative cases show stable cognition.

Aβ brain deposition begins in the preclinical stages of AD, increases during the MCI stage, and, by the time of the AD diagnosis, remains relatively stable as the disease progresses. Thus, it is a marker of the preclinical stages of the disease and correlates with the degree of cognitive impairment only in the preclinical stages and MCI, not during AD, while atrophy and synaptic dysfunction continue to increase and spread as clinical AD worsens and cognition deteriorates.

Hyperphosphorylated Tau Imaging:

In the healthy brain, the protein tau stabilizes neurotubules and is therefore essential for normal neural function. However, in AD and other neurodegenerative disorders, tau becomes abnormally hyperphosphorylated, dysfunctional, and misfolded, constituting the tangles observed neuropathologically in AD and other tauopathies. The imaging compounds that we mention here do not bind to the healthy, native form of tau but to the abnormally folded tau, thus allowing only the pathological form to be visualized. The first compound shown to bind to hyperphosphorylated tau is 18F-FDDNP, which binds to Aβ as well, but with less imaging sensitivity and specificity than the PIB-like compounds. It has shown increased binding in regions likely to have high tau, such as the medial temporal regions, which show relatively low 11C-PiB binding. In the initial stages of use in humans are several tau-binding compounds that seem to have imaging characteristics superior to FDDNP. These compounds include 11C-PBB3, 18F-T807, most recently known as 18F-AV-1451, and 18F-THK5117. 11C-PBB3 is photosensitive and therefore difficult to use in practice; it also has a high level of uptake in the superior sagittal sinus. The most experience exists with...
18F-AV-1451, which shows highly specific uptake in areas known neuropathologically to contain a large amount of tau in AD. These ligands have not yet been FDA approved for diagnostic use in AD.

While their decreased invasiveness makes the neuroimaging technologies very desirable, CSF biomarkers remain the most established and studied biomarkers in the diagnosis or AD. We will discuss them in more detail in the section below.

CSF Biomarkers

The core pathological hallmarks of AD are the intracellular accumulation of abnormally hyperphosphorylated tau protein and the extracellular deposits of Aβ peptide. Because the CSF is in direct contact with the extracellular space of the brain and usually reflects pathological changes in the brain, it seems like an optimal source of biomarkers.

Currently, the main biological biomarkers employed in AD diagnosis are total tau (t-tau), the isoforms of phosphorylated tau (p-tau181 and p-tau231), and b-amyloid peptide (Aβ42).

Data from clinico-pathological studies show that CSF levels of total Tau reflect the intensity of neuronal degeneration, while p-tau reflects tangle pathology and Aβ42 is inversely correlated with Aβ plaque counts at post-mortem examination.

CSF Markers of Aβ Deposition:

Several proteins, peptides, and enzymes involved in the amyloidogenic APP processing can be measured in the CSF. These include different truncated species of Aβ, Aβ14 to Aβ16 and Aβ17 up to Aβ42, soluble b-secretase cleaved APP (sAPPb), and Aβ oligomers. Among these, only CSF Aβ42 is well established as a biomarker for AD.

The measurement of Aβ in the CSF became an important candidate biomarker for AD after a report showing the secretion of Aβ in the CSF in 1992. However, subsequent reports showed no clear change of CSF total Aβ in AD. Immunoassays specific for Aβ42 were developed after it was discovered that the 42 amino acid form of Aβ, Aβ42, was prone to aggregate and the earliest Aβ species deposited in plaques. Numerous studies since 1995 have shown a marked reduction in CSF Aβ42 in patients with AD dementia, with a level approximately 50% of the age-matched cognitively normal individuals. The absolute cut-off value varies with the measurement technique used, with values between 450–650 pg/mL for ELISA and 192 pg/mL for the Luminex xMAP technique. However, the two techniques show a tight linear correlation. In a recent meta-analysis, this test was found to have a pooled sensitivity of 80% and specificity of 76% in distinguishing AD from control or non-AD dementia.

The lowering of CSF Aβ42 in AD is due to the peptide’s aggregation in the brain, with an inverse correlation between low levels of Aβ42 and postmortem plaque load in cortical regions, and it precedes AD dementia onset by at least 10 years. In addition to helping with the diagnosis of AD, CSF Aβ42 might be useful in MCI patients as well as for treatment response evaluation. Indeed, multiple studies have shown that more than 90% of MCI patients progressing to AD dementia have low CSF levels of Aβ42 at baseline, while stable MCI cases have normal CSF Aβ42. In addition, a transient lowering of CSF Aβ42 was reported in response to reduced Aβ production following BACE1 inhibitor treatment as well as in healthy volunteers.

However, inter-individual variations in total Aβ production (of all Aβ isoforms) exists, and some AD cases that are “high producers” may have false negative Aβ42 tests; that is, the decrease in CSF Aβ42 is masked by the overall higher Aβ production. Conversely, some non-AD cases that are “low producers” may have false-positive Aβ42 tests, with a level just above the cut-off. Some authors suggest correcting this by the use of the CSF Aβ42:Aβ40 ratio, where Aβ40 is around 10 times more abundant than Aβ42 and not affected by AD. The reduction of Aβ42 (but not Aβ40) in AD leads to a reduction in this ratio that is more marked than the reduction in Aβ42 alone. Further validation is needed, as well as determining a cutoff AD diagnostic value for this ratio.

CSF Markers of Tau:

While quite sensitive for AD pathology, a reduction of CSF Aβ42 levels may also occur in other diseases, such as Lewy body dementia, vascular dementia, and cerebral amyloid angiopathy without AD. Hence, although a decreased level of Aβ42 is suggestive of AD, it is not sufficient for a diagnosis of AD.
Total tau CSF levels are approximately 3 times higher in AD patients than in age-matched controls. The specificity of this isolated biomarker is low, as total Tau protein levels can also be elevated in other acute neurodegenerative diseases and brain lesions, such as head trauma, stroke, and Creutzfeldt-Jakob disease. On the contrary, p-tau protein (subtypes p-tau181 and p-tau231) is the most specific biomarker of AD, being normal in non-AD diseases, including those in which Tau protein levels may be increased.

High levels of CSF total tau and p-tau seem also to be related to a faster progression of hippocampal atrophy on MRI. These findings, however, need further validation.

**Correlation Between the Different Biomarkers**

Taken individually, each biomarker and imaging technique provides some information on one aspect of AD pathology. It is worthwhile to assess the correlation—and discordance—between them.

In the Aβ pathway, the lowering of CSF Aβ42 in AD is due to the aggregation of peptide in the brain, with an inverse correlation between low levels of Aβ42 and in vivo PiB binding in cortical regions. Overall, 88% of subjects in one study had concordant amyloid biomarker results, with either negative or positive amyloid PET scans and CSF Aβ42 levels. A few had discordant amyloid biomarker results, with either normal CSF Aβ42 levels but positive amyloid PET scans (5.4%), or positive (low) CSF Aβ42 but normal amyloid PET (6.6%). The existence of cases with discordance between CSF and PET amyloid deposition in MRI and 18F-FDG characteristics, leading to the conclusion that these changes may be independent of Aβ deposition in the brain. However, participants with abnormal Aβ had a greater rate of worsening to dementia and progressive worsening of MRI and 18 F-FDG parameters, not observed in the SNAP group, in a 15-month follow-up. Over a 14-year follow-up, the progression to dementia of the SNAP group was only slightly higher than that of Aβ-negative, MRI-normal participants and lower than those with Aβ on PET and normal MRI.

On the other hand, a large study comparing PET and CSF markers showed that amyloid PET was more strongly related to CSF tau and cognitive decline than CSF Aβ42, while CSF Aβ42 was more strongly related to possession of the apolipoprotein E (APOE) e4 allele than amyloid PET. Other studies have shown that patients who are amyloid PET-positive have higher CSF t-tau and p-tau levels, but the correlations with CSF t-tau and p-tau are weaker than the strong inverse correlation found between amyloid ligand retention and CSF Aβ42.
A recent series analyzing the relationship between AD pathology in cortical brain biopsy and AD biomarkers in 182 AD patients showed that the amount of amyloid plaques and hyperphosphorylated Tau in cortical brain biopsies were associated with low CSF Aβ42 and high CSF levels of tau markers, respectively. Another series reported a 94% concordance between CSF biomarkers and neuropathological diagnosis. An AD biomarker profile (low Aβ42 associated with high levels of CSF total tau and p-tau) also distinguishes with high accuracy (up to 95% sensitivity) MCI patients who will progress to AD from MCI patients who will remain cognitively stable during the follow-up and from healthy controls.

AD biomarkers might also have some prognostic value, as AD patients with extreme alterations in CSF biomarkers (Aβ42 reduction and increased total tau and p-tau) appear to progress unfavorably, with more severe cognitive decline, poor response to anticholinesterase treatment, and higher mortality.

Finally, some authors advocate the use of the p-tau/ Aβ42 ratio and report a sensitivity of 91.6% and a specificity of 85.7% for AD compared to neuropathology. In one study, it was also the best biomarker for differentiating AD from the behavioral variant of frontotemporal lobar degeneration and from semantic dementia, with a sensitivity of 91.7% and 98.3%, respectively, and a specificity of 92.6% and 84.2%, respectively.

Other Biomarker Candidates

In a recent meta-analysis of all CSF and blood biomarkers for the diagnosis of AD, Olsson et al reviewed cohorts of patients with AD versus controls or patients with mild cognitive impairment due to AD versus those with stable mild cognitive impairment (i.e., not progressing to dementia at a follow-up of at least 2 years). They extracted data for markers of APP metabolism (Aβ42, Aβ40, Aβ38, and α and β cleaved soluble amyloid precursor protein [sAPPα and sAPPβ]), neurodegeneration (t-tau, neurofilament light protein [NFL], neuron-specific enolase [NSE], visinin-like protein 1 [VLP-1], and heart fatty acid binding protein [HFABP]), tangle pathology (p-tau), glial activation (YKL-40, monocyte chemotactic protein 1 [MCP-1], and glial fibrillary acidic protein [GFAP]) and blood–brain barrier function (CSF to serum albumin ratio) in the CSF and blood (serum or plasma).

The authors found that the core biomarkers differentiated AD from controls with good performance. CSF total tau and p-tau were on average 2.54 times (95% CI 2.44–2.64, p<0.0001), and 1.88 times (95% CI 1.79–1.97, p<0.0001) higher, respectively, than in controls, while the level of Aβ42 was almost 50% lower (0.56, 95% CI 0.55–0.58, p<0.0001) in AD patients than in controls. These markers also allowed differentiation between cohorts with mild cognitive impairment due to AD and those with stable mild cognitive impairment with average ratios of 0.67 for CSF Aβ42, 1.72 for p-tau, and 1.76 for t-tau.

In addition, CSF NFL was helpful in differentiating between AD patients and controls (2.35, 95% CI 1.90–2.91, p<0.0001). The plasma levels of t-tau were also significantly higher in AD patients than in controls (1.95, 95%CI 1.12–3.38, p=0.02), but the variation in the few available studies was large; more data are needed to verify this association. CSF NSE, VLP-1, HFABP, and YKL-40 showed moderate differences between AD patients and controls (average ratios 1.28–1.47). Other assessed biomarkers had only marginal effect sizes or did not differentiate between control and patient samples.

The authors suggested that t-tau, p-tau, Aβ42, and NFL in the CSF should be used in clinical practice and clinical research. However, there is no established cutoff for these tests. Indeed, there is significant variation in how different laboratories establish cutoffs for biomarker concentrations to differentiate patients with AD from controls. Furthermore, there is substantial variability in biomarker concentrations between laboratories and assays.

A special note should be made that, in the meta-analysis from Olsson et al, the blood level of Aβ42 was not useful for distinguishing between AD and controls (average ratio 1.04, 95% CI 0.96–1.12, p=0.32) or between mild cognitive impairment due to AD and stable mild cognitive impairment (average ratio 0.81, 95% CI 0.53–1.24, p=0.32). Similarly, plasma or serum concentrations of Aβ40 did not differ significantly between patients with AD and controls (average ratio 1.04, 95% CI 0.98–1.11, p=0.17 (136). No data were available for serum or plasma P-tau.
Clinical Practice

In autosomal-dominant AD, where the timing of the onset of dementia can be predicted with a certain level of accuracy, CSF Aβ1–42 declines 25 years before onset, followed by amyloid deposition, as measured by PET imaging 15 years before onset, along with increased CSF tau and hippocampal atrophy. This is followed by cerebral hypometabolism on 18F-FDG-PET about 10 years before onset.25, 102 A similar sequence seems to be present with Aβ deposition in sporadic, late onset AD, although the etiologic mix in the more advanced age group yields more complex biomarker results.138 P-tau deposition occurs in AD, but its timing in relation to Aβ deposition or to the onset of clinical symptoms has not been determined by in vivo studies.25

The amyloid biomarkers CSF Aβ42 and amyloid PET both show a high diagnostic ability to identify AD during the earlier stages of the disease. These biomarkers also demonstrate high concordance, with approximately 90% of cases being either positive or negative for both biomarkers. The high concordance for the amyloid biomarkers suggests that they may be used interchangeably to aid in clinical diagnostic work-up or patient enrichment in clinical trials.

Core CSF biomarkers for AD are a reduction in Aβ42, with an increase in t-tau and p-tau. The sensitivity and specificity of the combined use of CSF Aβ42, t-tau, and p-tau for the diagnosis of AD in the dementia or MCI stage reaches 85%–90%.80 Values that are close to the cutoff should be interpreted with caution, as there is a continuum of values and an overlap between controls and patients with AD or MCI.6 Furthermore, no clinically available cutoff has been determined for any of these levels, and each institution should establish an internally validated diagnostic cutoff value.

The choice between amyloid PET and CSF biomarkers as diagnostic tools in the clinic will depend on the availability, training status, and willingness among clinicians to perform lumbar puncture, the availability of and distance to PET scanners and cyclotrons, and finally, financial considerations that payers have to make (i.e., CSF analysis is more affordable than a PET scan).6 Regarding side-effect profiles, post-lumbar puncture headaches, the main complication following a lumbar puncture, have an incidence of 1%–3%,139–141 which is in the same range as the risk of headaches following amyloid PET.5

In 2007, the International Working Group (IWG-1) proposed research criteria for “prodromal Alzheimer’s disease” requiring the presence of episodic memory impairment and at least one abnormal biomarker, either of molecular pathology (reduced CSF Aβ42, elevated CSF tau, or amyloid PET deposition) or topography (medial temporal lobe atrophy or FDG hypometabolism).143

Revised in 2014, the IWG-2 criteria allow for prodromal AD to be diagnosed in the presence of cognitive impairment in domains other than memory, or in the presence of either increased amyloid PET deposition or the combination of lowered CSF amyloid-β1-42 and elevated CSF tau.144 In 2011, the National Institute on Aging/Alzheimer’s Association (NIA-AA) reviewed diagnostic criteria for AD dementia.145 While recognizing the usefulness of biomarkers and calling laboratories to establish internally qualified cutoff values, biomarkers were not recommended for routine diagnostic purposes. However, these can increase confidence in a clinical diagnosis of AD and can be useful in certain circumstances, such as early-onset dementia and atypical presentations of AD in which the differential diagnosis includes other neurodegenerative diseases.

In regard to MCI, the NIA-AA proposed new research/clinical criteria for MCI due to AD (MCI-AD).146 These criteria allow for cognitive impairment in any domain (not only episodic memory) and incorporate combinations of amyloid (CSF or PET) or “neuronal injury” markers (medial temporal lobe atrophy, CSF tau, temporo-parietal FDG-PET hypometabolism). When combined, these markers allow several designations: (i) a high likelihood of MCI due to AD, i.e., MCI and both abnormal amyloid and neuronal markers; (ii) a low likelihood of MCI due to AD, i.e., MCI but normal/negative amyloid and neuronal markers; (iii) an intermediate likelihood of MCI due to AD where information from only one biomarker—either a neuronal injury marker or amyloid marker—is available, and that biomarker is abnormal, and; (iv) uninformative, i.e., MCI but biomarkers are unavailable, conflicting, or indeterminate. In cases in which amyloid markers are negative but measures of neuronal injury are positive, the term MCI suspected non-Alzheimer’s pathology (MCI sNAP) has been proposed.125
It is uncertain how these criteria compare in their ability to detect MCI due to underlying AD and to predict the subsequent development of AD dementia, how easily each can be operationalized for use in multicenter cohort studies, and what can be concluded from cases with discordant biomarker results. Their use in clinical routine diagnosis of MCI cannot be recommended.

The accumulated data from clinical studies do not support the association of any specific biomarker of AD with the assumption of progression from normal cognition to AD in asymptomatic subjects; thus, the concept of “preclinical AD” is restricted only to research and cannot be translated into recommendations for clinical practice2,147 at this time.

**Conclusion**

The failure of many phase III studies has highlighted the strong need for biomarkers of AD to improve the specificity of the diagnosis, thus ensuring that non-AD demented patients are excluded from AD trials as well as to allow an earlier diagnosis and attempt a disease-modifying treatment earlier in the pathological process to improve the likelihood of success. In this lesson, we have reviewed the available imaging and biological markers of AD and their clinical applications. While these imaging findings and biomarkers are not yet part of the diagnostic criteria of AD, they can increase confidence in a clinical diagnosis of AD and can be useful in certain circumstances, such as early-onset dementia and atypical presentations of AD in which the differential diagnosis includes other neurodegenerative diseases.

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References


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**Multiple-Choice Questions**

69. Which one of the following statements is true?
   A. AD clinical diagnosis is specific enough for research and clinical purposes.
   B. AD diagnostic criteria include the use of biomarkers.
   C. Biomarkers increase the sensitivity and specificity of AD diagnosis, but they are not yet included in the diagnostic criteria.
   D. None of the above.

70. Which one of the following statements regarding biomarkers of AD is correct?
   A. CSF Aβ42 decreases only in AD and is thus very specific.
   B. CSF total tau increases only in AD and is very specific.
   C. The combination of reduced Aβ42 and increased total tau and p-tau in the CSF is the most sensitive and specific for AD.
   D. The combination of reduced Aβ42 and increased total tau and p-tau in blood is the most sensitive and specific for AD.

71. Regarding the correlation between different biomarkers, all of the following statements are correct, except:
   A. There is a 90% concordance between a CSF Aβ42 reduction and amyloid retention on PET scans in patients with AD.
   B. AD core markers increase the risk of evolution from MCI to AD.
   C. The risk of evolution from MCI to AD can be accurately predicted in any individual with AD core markers.
   D. The CSF Aβ42 level changes 10 years before the amyloid PET scan.

72. Regarding imaging in AD:
   A. Tau imaging by PET scan has been FDA approved for the diagnosis of AD.
   B. Aβ imaging by PET scan has been FDA approved for the diagnosis of AD.
   C. Brain MRI shows frontal and temporal atrophy.
   D. Perfusion SPECT has much better sensitivity and specificity than metabolism for the diagnosis of AD.
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Biomarkers in Alzheimer’s Disease

By Carla Bejjani, MD; Raja Mehanna, MD; and Asim Shah, MD

ID#: L003381

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The current diagnosis of AD relies solely on clinical criteria. The failure of many phase III studies revealed a strong need for biomarkers of AD to improve the specificity of the diagnosis. In this lesson, we review the available imaging and biological markers of AD to help address the gap in knowledge about biomarkers in AD.

Key Point 1: Need for Biomarkers
There is a need for biomarkers of AD to allow better patient selection and earlier intervention in clinical trials.

Key Point 2: CSF Biomarkers
The core cerebrospinal fluid (CSF) biomarkers for AD are a reduction in Aβ42 and increases in T tau and P tau.

Key Point 3: Concordance between Imaging and CSF Biomarkers
Amyloid biomarkers CSF Aβ42 and amyloid PET have a high and early diagnostic ability, with high concordance between the 2 tests.

Key Point 4: The Use of Biomarkers
Biomarkers increase the sensitivity and specificity of AD diagnosis, but they are not yet included in the diagnostic criteria.

Key Point 5: Preclinical AD
A concept of “preclinical AD” is restricted only to research and cannot be translated into recommendations for clinical practice.
Substance Use During Pregnancy

Ariadna Forray, MD

KEYWORDS: Pregnancy • Substance use disorder • Breastfeeding • Tobacco

LEARNING OBJECTIVES: Clinicians will (1) review the different types of substance abuse that occurs in pregnant women; (2) understand the way in which substance use affects a developing pregnancy; (3) consider the common co-occurring conditions and disorders that impact pregnant women with substance use disorders, and; (4) understand the ways that breastfeeding may assist in relapse prevention.

LESSON ABSTRACT: Prenatal substance use is a critical public health concern that is linked with several harmful maternal and fetal consequences. The most frequently used substance in pregnancy is tobacco, followed by alcohol, cannabis and other illicit substances. Unfortunately, polysubstance use in pregnancy is common, as well as psychiatric comorbidity, environmental stressors, and limited and disrupted parental care, all of which can compound deleterious maternal and fetal outcomes. There are few existing treatments for prenatal substance use and these mainly comprise behavioral and psychosocial interventions. Contingency management has been shown to be the most efficacious of these. The purpose of this review is to examine the recent literature on the prenatal use of tobacco, alcohol, cannabis, stimulants, and opioids, including the effects of these on maternal and fetal health and the current therapeutic options.

COMPETENCY AREAS: This lesson serves to educate clinicians regarding substance use disorders in pregnancy. Clinicians will gain medical knowledge in identifying risks that pregnant patients with a substance use disorder may face. This lesson will review the evidence regarding treatment options and relapse prevention in pregnant women.
Introduction

In the United States, women comprise 40% of those with a lifetime drug use disorder and 26% of those who meet criteria for both an alcohol and drug use disorder during the prior 12 months. Furthermore, women are at highest risk for developing a substance use disorder during their reproductive years (18–44), especially ages 18–29. This means that women who are pregnant or soon to become pregnant are at increased risk for substance abuse. According to a national survey conducted in the United States in 2012, 5.9% of pregnant women use illicit drugs, 8.5% drink alcohol and 15.9% smoke cigarettes, resulting in over 380,000 offspring exposed to illicit substances, over 550,000 exposed to alcohol and over one million exposed to tobacco in utero. Similar patterns of use have been observed in Europe and Australia. The most commonly used substance in pregnancy is nicotine, followed by alcohol, marijuana and cocaine. However, polysubstance use is as high as 50% in some studies. Recently, there has been an increase in opiate use in pregnancy. Between 2000 and 2009, the United States saw a five-fold increase in opiate use in pregnancy, coincident with an “epidemic” of opiate prescription misuse.

There is little information available on the extent of substance use, other than tobacco, among pregnant women in low-income and middle-income countries. The overall prevalence of tobacco use in these countries is 2.6%, with some countries having much higher maternal rates—up to 15%. While data on illicit substance use in pregnancy is lacking for most middle- and low-income countries, according to the World Health Organization, cannabis is the most common illicit drug worldwide, followed by amphetamine-type stimulants and opiates, and, as such, they are likely to be used by women of reproductive age. The limited data available for Africa is from South Africa, and indicates that between 3.6 and 8.8% of pregnant women use illicit substances and 19.6% use alcohol. The most commonly used illicit substances in South Africa include methamphetamine and cannabis. Opiate use has also increased in places like Africa and Asia, and is likely to become more prevalent in pregnancy.

Prenatal substance use can bring about several deleterious consequences for both mother and baby, as described in detail below. The concern for the impact of substances on the developing fetus can motivate some women to curb their drug and alcohol use during pregnancy. In the only prospective study on prenatal substance use, 96% of women with heaving drinking, 78% of women with marijuana use, 73% of women with cocaine use, and 32% of cigarette smokers succeeded in achieving abstinence during pregnancy. Offsetting the reduction in pregnancy-related use is the dramatic rise in substance use from 6 to 12 months postpartum. The study showed relapse in 58% of abstinent smokers, 51% of abstinent women who used alcohol, 41% of abstinent women who used marijuana and 27% of abstinent women who used cocaine in the 3 months following delivery. Thus, while the levels of abstinence in pregnancy may be high, the impact of this is diminished due to the high rates of relapse postpartum. Unfortunately, maternal relapse happens at a time of high childcare needs and when infant development is dependent on maternal bonding. It is also important to note that this was a study conducted in the United States and that the levels of abstinence may not be equivalent in other countries, especially middle- and low-income countries where women may encounter significant socioeconomic stressors, low levels of education, and limited available treatments for substance use.

As evidenced by these data, substance use in pregnancy is still a critical public health concern. The purpose of this review is to provide a brief overview of the pregnancy outcomes, neonatal and long-term developmental consequences of prenatal substance use, and current available treatments for pregnant women.

Adverse Effects of Substance Use in Pregnancy

Heavy alcohol use in pregnancy has been associated with a range of negative birth outcomes, including increased risks of miscarriage, stillbirth and infant mortality, congenital anomalies, low birthweight, reduced gestational age, preterm delivery, and small-for-gestational age. The evidence for low to moderate alcohol use in pregnancy has either been inconclusive or shown no increased risk for these adverse pregnancy outcomes. Alcohol use in pregnancy has the most well established adverse fetal health effects and is associated with the development of fetal alcohol...
spectrum disorders and adverse neurodevelopmental outcomes. In addition, prenatal drinking is associated with long-term effects, such as cognitive and behavioral challenges, adverse speech and language outcomes, executive functioning deficits in children, and psychological consequences in adulthood.

Smoking during pregnancy exerts direct adverse effects on birth outcomes, including damage to the umbilical cord structure, miscarriage, increased risk for ectopic pregnancy, low birthweight, placental abruption, preterm birth, and increased infant mortality. Also of concern are the deleterious health effects of second-hand smoke on newborns, which include higher rates of respiratory and ear infections, sudden infant death syndrome, behavioral dysfunction and cognitive impairment. Additionally, women who were smokers before pregnancy might stop breastfeeding early so that they can take up smoking again.

Some pregnant women view cannabis use as harmless in pregnancy; however, it has been linked with several deleterious effects, including preterm labor, low birthweight, small-for-gestational age, and admission to the neonatal intensive care unit. Prenatal cannabis use has also been linked with adverse consequences for the growth of fetal and adolescent brains, reduced attention and executive functioning skills, poorer academic achievement and more behavioral problems. The adverse effects of marijuana are frequently observed with comorbid substance use, and are greatest in heavy users.

The extent of the adverse effects of cocaine use in pregnancy has been overestimated at times. However, there have been several large and thorough studies recently, which have all identified several risk factors associated with cocaine use during pregnancy, including premature rupture of membranes, placental abruption, preterm birth, low birthweight, and small for gestational age infants. There have been inconsistent reports on the long-term effects of prenatal cocaine exposure on language, motor, and cognitive development, with a few studies describing positive findings and some studies reporting very little or no effects. This inconsistency is probably connected to the confounding effects of the postnatal environment, including unsteady and disordered home environments, dysfunctional parenting, and heavy maternal polysubstance use. Similar to cocaine use in pregnancy, methamphetamine use is linked with shorter gestational ages, lower birthweight, fetal loss, developmental and behavioral defects, preeclampsia, gestational hypertension, and intrauterine fetal death.

Opioid use in pregnancy is correlated with a greater risk of low birthweight, respiratory problems, third trimester bleeding, toxemia and mortality. Maternal opiate use is associated with an increased risk of neonatal abstinence syndrome (NAS), whereby opiate exposure in utero triggers a postnatal withdrawal syndrome. Anywhere from 45% to 94% of infants exposed to opioids in utero, including methadone and buprenorphine, can be affected by NAS. NAS results in substantial neonatal morbidity and increased healthcare utilization and consists of an array of signs and symptoms, including irritability, feeding difficulties, tremors, hypertonia, emesis, loose stools, seizures, and respiratory distress. Opioid exposure in pregnancy has also been associated with postnatal growth deficiency, microcephaly, neurobehavioral problems, and sudden infant death syndrome. Cigarette smoking, which is very common in pregnant women with an opioid use disorder (77%–95%), may confound the effect of opioid use on poor pregnancy outcomes.

A significant point to take into account is that the undesirable consequences of prenatal substance use are confounded by the frequency of coexisting substance use and comorbid psychiatric illness. Women with substance use disorders also frequently experience inadequate prenatal care, poor nutrition, chronic medical problems, poverty, and domestic violence. Furthermore, substance use in pregnancy may also result in an early dysfunctional maternal-infant relationship that can potentiate the negative effects of prenatal drug exposure.

Treatment of Substance Use in Pregnancy

There are only a small number of effective therapies for substance use in pregnancy, which primarily involve behavioral counseling (see Table 1). Brief interventions, in particular those that utilize motivational interviewing, have been shown to reduce prenatal alcohol use. A recent randomized trial utilizing a telephone-based brief intervention suggests that this method may achieve similar results to the in-person intervention method of
moderating prenatal drinking. Some additional interventions to reduce prenatal drinking that have recently been described include screening via non-healthcare community workers, counseling by midwives, and multimedia and educational efforts aimed at improving awareness.

As with alcohol, behavioral counseling is the main treatment for smoking cessation and relapse prevention in pregnant women. Unfortunately, psychotherapeutic interventions have had only moderate success. Pharmacological treatments for smoking cessation have not been evaluated with respect to their safety and efficacy in pregnant and postpartum women. Randomized clinical trials with nicotine replacement therapy in pregnant women have demonstrated limited efficacy in increasing the rates of abstinence. The most successful intervention for prenatal smoking cessation is contingency management (CM) with financial incentives, which has also reportedly improved birth outcomes.

Treatments specifically aimed at prenatal cannabis use are lacking. The current recommendation for lowering the use of cannabis in pregnancy includes the screening of pregnant women to increase the early identification of cannabis use. Motivational interviewing (MI) and CM therapies have had some success in reducing marijuana use in women, but they have not been evaluated specifically with pregnant users. Thus, novel interventions that explicitly target cannabis use are vital, particularly given the current tendency towards marijuana legalization.

Existing evidence-based treatments for cocaine use in pregnancy include CBT, MI and CM. As with smoking, CM is the intervention that shows most potential for treating cocaine-using pregnant women. A randomized trial found that CM was associated with much longer duration of cocaine abstinence, higher number of cocaine-negative urine tests, and a greater proportion of documented abstinence when compared to community reinforcement approach and twelve-step facilitation. Currently, there are no evidence-based pharmacological treatments for prenatal cocaine use. Nevertheless, a recent randomized, placebo-controlled trial supports the use of oral micronized progesterone as an intervention for postpartum cocaine use. The study showed that women randomized to placebo had more self-reported cocaine use compared to women receiving micronized progesterone during the 12 weeks of the trial. While these are preliminary findings and will require confirmation in a larger clinical trial, they show promise for the application of progesterone in postpartum women to reduce their cocaine use. Treatments for other stimulant use, such as methamphetamine, are limited. Research into reinforcement-based therapy (RBT) combined with a women-focused intervention among pregnant methamphetamine users reported a reduction in methamphetamine use over time. However, there were no substantial distinctions between the intervention and control conditions, not unlike another study using RBT to treat stimulant use in pregnancy. RBT seems to have potential as an intervention for methamphetamine use but more research is required.

### Table 1: Description of Behavioral Interventions for Substance Use Disorders

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
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<tbody>
<tr>
<td>Contingency management (CM)</td>
<td>Based on the principle of positive reinforcement as a means of operant conditioning to influence behavior change. The premise behind CM is to systematically use reinforcement techniques, usually monetary vouchers, to modify behavior in a positive and supportive manner. Originally used for the treatment of cocaine users, it has since been used for opioids, marijuana, cigarettes, alcohol, benzodiazepines, and other drugs.</td>
</tr>
<tr>
<td>Motivational interviewing (MI)</td>
<td>A patient-centered, collaborative and highly empathic counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence. It draws from the transtheoretical model of change in order to improve treatment readiness and retention.</td>
</tr>
<tr>
<td>Cognitive Behavioral Therapy (CBT)</td>
<td>A psychotherapeutic treatment that uses an easy-to-learn set of strategies to help patients understand the situations that lead them to undesirable thoughts, feelings, or behaviors, to then avoid those situations when possible, and to deal more effectively with such situations when they occur. The goal of these strategies is to break old patterns of responding and replace them with new ones.</td>
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Methadone maintenance is the standard care for pregnant women with opiate use disorders. Conversion from illicit opioid use to opioid maintenance therapy in a medically supervised setting decreases maternal and neonatal morbidity. Methadone maintenance offers greater relapse prevention with a steady opioid dosing regimen, reduces risk-taking behavior, enhances compliance with prenatal care, and leads to better neonatal outcomes. On the other hand, medication-assisted withdrawal, that is detoxification by gradually reducing the dose of an opioid substitute medication, is associated with a high opioid relapse rate and higher fetal morbidity and mortality rates. Buprenorphine has recently emerged as another potential therapy for opioid use in pregnancy. A randomized controlled trial that compared methadone and buprenorphine in pregnant opioid users showed that infants whose mothers received buprenorphine needed less treatment for NAS, substantially lower doses of morphine to treat NAS symptoms, and had shorter stays in hospital, compared to the infants of women given methadone. Notably, buprenorphine had lower retention rates with flexibly delivered doses and low fixed doses compared to methadone. However, buprenorphine and methadone are equally effective when given as fixed medium or high doses. CM has likewise been reported to be effective in treating opioid use in pregnancy, by significantly increasing abstinence and treatment attendance compared to controls. Thus, CM appears to be an important addition to methadone or buprenorphine treatment in pregnant women.

Breastfeeding and Postpartum Substance Use

Breastfeeding has the potential to be a useful tool for substance use in the postpartum period. Breastfeeding is the only available intervention shown to reduce NAS severity in opioid-exposed newborns. Breastfeeding might also be protective for postpartum relapse. For example, among breastfeeding smokers, 10% stop breastfeeding because of smoking, and over half of recent or current smokers reported that smoking affected their infant feeding decision. In addition, non-current smokers are more likely to initiate and continue breastfeeding compared to current smokers. Therefore, the promotion of breastfeeding might prevent or delay postpartum relapse.

While studies evaluating the potential role of breastfeeding as an intervention for substance use postpartum are limited, the rationale for such interventions is clear. Lactation reduces the HPA response to physical stress. A behavior that promotes relaxation and reduces stress would be helpful to women with substance use disorders since psychosocial stress increases cravings. While hormones released during lactation may mediate stress reduction, such hormones have other properties that may help women cope with addiction. Considerable attention has been dedicated to oxytocin, a hormone released during delivery and lactation. Oxytocin administration is under investigation for treatment of drug and alcohol use disorders. In addition, lactation is positively associated with cognitive and motor development in the infant. It is well known that stable attachment among children increases resiliency and protects against the development of addiction later in life. Thus, an intervention that promotes lactation and intimacy through skin-to-skin contact may enhance stable attachment, and have the intergenerational benefit of protecting offspring from the development of addictive and other problematic behaviors.

Conclusions

Substance use in pregnancy remains a significant public health problem, which can lead to several harmful maternal and neonatal outcomes. Which drug is being used and the degree of use, as well as the point of exposure, all influence the effects of drug use in pregnancy. In addition to the direct effects of drug exposure in utero, several other variables are associated with deleterious maternal and infant consequences, including psychiatric comorbidity, polysubstance use, limited prenatal care, environmental stressors and disrupted parental care. In conjunction, these factors can negatively influence pregnancy and infant outcomes, and should be taken into account when developing interventions for prenatal substance use treatments. Many of the health problems associated with substance use in the prenatal period could be avoided given effective and well-timed medical care or intervention. Empirically-driven interventions for
prenatal substance are needed. While there are few treatment options for substance use in pregnancy, CM seems to show the greatest promise as an effective therapy for the substances in which it has been studied. Future research needs to focus on developing tailored, safe, and acceptable treatments that can capitalize on pregnancy as a “teachable” moment that can motivate women to adopt risk-reducing health behaviors.124–127

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Hatherleigh’s Note: Additional typeface treatment was added to text for emphasis. Supplementary title page information, CME, Best Practices, and medication trade names were also included.

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Competing interests: No competing interests were disclosed.


References


Multiple-Choice Questions

73. According to the lesson, what percentage of pregnant women drink alcohol?
   A. 8.9%
   B. 14%
   C. Less than 1%
   D. 6%

74. All of the following are outcomes of heavy alcohol use in pregnancy, except:
   A. miscarriage.
   B. high birthweight.
   C. preterm delivery.
   D. infant mortality.

75. What are some common co-occurring problems from pregnant women suffering from substance abuse?
   A. Poor nutrition
   B. Poverty
   C. Domestic violence
   D. All of the above

76. What is the main treatment for smoking cessation in pregnant women?
   A. Family therapy
   B. Antidepressant medication
   C. Nicotine patches or gum
   D. Behavioral counseling
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Substance Use During Pregnancy
By Ariadna Forray, MD
ID#: L003382

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview
This lesson reviews how pervasively substance use disorders can affect pregnant women. By reviewing the different types of substances that are most frequently used by women, the authors explore the different ways this can impact a fetus during pregnancy. Looking at co-occurring mental disorders, as well as life circumstances, the authors paint a full picture of the challenges clinicians will face when working with pregnant women with substance use disorders. Treatment of these issues can be difficult, and research has only begun to explore the effects different factors can have on a woman’s chance of recovery.

Key Point 1: Prevalence of Fetal Exposure to Substances
Over one million fetuses are exposed to illicit drugs, alcohol, and tobacco every year. Over 380,000 offspring exposed to illicit substances, over 550,000 exposed to alcohol and over one million exposed to tobacco in utero.

Key Point 2: Emotional Sequela
Pregnant women with substance use disorders also frequently cope with other negative life circumstances. Poverty, domestic violence, poor nutrition, chronic medical conditions, and poor access to healthcare are common issues faced by pregnant women with substance use disorders.

Key Point 3: Breastfeeding & Relapse Prevention
Breastfeeding may aid in the cessation of behaviors and relapse prevention. Studies show that among breastfeeding smokers, 10% stop breastfeeding because of smoking, and over half of recent or current smokers reported that smoking affected their infant feeding decision.

Key Point 4: Necessity of Early Intervention in Pregnant Women
Many of the health problems associated with substance use in the prenatal period could be avoided given effective and well-timed medical care or intervention. Research to provide evidence-based treatments for substance use disorders in pregnant women are needed.
Knowledge Transfer in the Field of Parental Mental Illness: Objectives, Effective Strategies, Indicators of Success, and Sustainability

Camilla Lauritzen, PhD; and Charlotte Reedtz, PhD

No commercial support was used in the development of this CME lesson.

**KEYWORDS:** Health system improvement • Children of mentally ill parents • Effective strategies • Sustainability

**LEARNING OBJECTIVES:** Readers will review the need and complexities of establishing, implementing, and sustaining interventions to reduce the transference of mental illness from parents suffering from mental illness to their children. This lesson explores aspects of knowledge transfer, indicators of success, and continuance.

**ABSTRACT:**

**Background:** Mental health problems are often transmitted from one generation to the next. However, transferring knowledge about interventions that reduce intergenerational transmission of disease to the field of parental mental illness has been very difficult. One of the most critical issues in mental health services research is the gap between what is generally known about effective treatment and what is provided to consumers in routine care.

**Discussion:** In this article, we discuss several aspects of knowledge transfer in the field of parental mental illness. Effective strategies and implementation prerequisites are explored, and we also discuss indicators of success and sustainability.

**Summary:** Altogether, this article presents a rationale for the importance of preventive strategies for children of mentally ill parents. Furthermore, the discussion shows how complex it is to change clinical practice.

**COMPETENCY AREAS:** This lesson aims to fill the gap of knowledge in the care of parents with mental illness to help mitigate the transference of psychiatric disorders to their children. This authors highlight the necessity of working in interdisciplinary teams to share information, the need for clinicians to take preventative steps to help break the cycle of mental illness that is transferred from parent to child, and the challenges to systemically realize these goals in clinical practice.
Background

Knowledge transfer can be defined as: The process which one unit – for example; an individual, a group, a department or an organization – is affected by the experience of another. It is important to highlight that providing information, presenting facts, arranging informative courses or even giving lectures is not the same as knowledge transfer. This is because knowledge alone is not necessarily sufficient in order to create behavior change. In essence, knowledge transfer is about facilitating behavior change. One way of explaining knowledge transfer is to regard it as the process of organizations seeking to improve performance by implementing a new practice.

How is knowledge transferred from one unit or organization to another? There are several factors that can facilitate or impede knowledge transfer in organizations and it is definitely possible to design organizations and procedures to promote knowledge transfer. This is, however, a very complex area, consisting of many important mechanisms. The literature is extensive on this field, and we will discuss the most important mechanisms of knowledge transfer later in this article, but for now let’s just agree that there are many issues to address if you want to understand the mechanisms of knowledge transfer.

The Field of Parental Mental Illness:

Many studies have documented that mental illness is very common. Mental illness is defined as a psychological pattern, potentially reflected in behavior, that is generally associated with distress or disability and is not considered part of normal development. According to the DSM-IV criteria, the term mental disorder refers to a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual, is associated with present distress or disability and represents a manifestation of a behavioral, psychological, or biological dysfunction in the individual. The most common mental health problems are anxiety, depression and substance abuse issues. In a 2009 report on mental illness in Norway, The Norwegian Institute of Public Health (2009) estimated that up to 50% of the population will suffer from mental health problems at some point during their lifetime.

Adults with mental health problems are not less likely to be parents then the rest of the population. Several international studies the past two decades have indicated that children with mentally ill parents are at risk of developing mental health problems themselves. Parental mental illness is considered a powerful risk-factor, with a potential of serious impact for the children. For instance: parents with depression have more difficulties in interaction with their children, are more intrusive, less involved and less responsive.

More than one third of these children develop serious and long-lasting problems. Early in life, these children run a higher risk of abuse and neglect, depression, eating disorders, conduct problems and academic failure. Later in life, they are at a higher risk of depression, anxiety disorders, substance abuse, eating problems and personality disorders.

Maternal symptoms of anxiety and depression increased the risk of emotional and disruptive problem behaviors in children as early as 18 months of age, according to new research findings from the Norwegian Institute of Public Health. And these problems are often found to be long lasting.

It is especially when parental mental illness is present during the early years of life that it triggers dys-regulated emotion patterns, negative emotionality and insecure attachment. A lot of documentation exists on the serious effects parental mental illness may have on the early developmental stages of a child’s life. It is safe to say that early intervention is essential to counteract permanent damage to the child’s developmental path.

Parental mental illness may interrupt the neurological development in offspring. Since the brain is not fully developed when we are born, the experiences a child has growing up will have direct effect on the development of the brain. Children of mentally ill parents are in many cases exposed to traumatic childhood experiences, for example: they can be witnesses to violence, or they may have been subject to abuse or neglect. This is commonly referred to as developmental traumas. Developmental traumas result from growing up in a context of ongoing danger, maltreatment, unpredictability, and/or neglect. Developmental traumas tend to surface as several disorders, i.e., regulatory disorder during infancy, attachment disorders, hyperkinetic conduct disorder at school age, or combined conduct and emotional disorders during adolescence.
that live under stressful conditions over time, will produce a lot of stress hormones and the child is in a way becoming programmed into a state of constant emergency preparedness. The child’s cognitive resources are tied up in being in a state of emergency, and this delays and impairs the child’s development in other areas.23, 24

Regulatory competence is a key concept. Emotional regulation is developed early in life in interaction with caregivers. Emotional regulation is a complex process involving: the subjective experience (feelings), cognitive responses (thoughts), physiological responses (for example heart rate or hormonal activity), and behavior (such as bodily actions or expressions).25 Children who have been neglected or abused have been found to have a dysfunctional self-regulatory competence.23 The impact parental mental illness may have on offspring is commonly ignored within the adult mental health services,26 even though there is thorough documentation that Parental mental illness is a powerful risk factor for children. The objective of including a focus on the patient’s children is linked to prevention, because there are measures that can be taken to counteract the risk, for instance by implementing a prevention perspective in adult mental health services. There is a substantial amount of research documenting that teaching parents positive parenting strategies to promote children’s self-confidence, pro-social behaviors, problem-solving skills and academic success reduces the risk for those children.27, 28

It also involves preventing added burden to the parents disease, because research has documented that treatment alone is not as effective as when it is combined with family focused strategies.29 And thirdly, and hopefully as a result of this; preventing mental illness from being transmitted from one generation to the next.10

Discussion

There are several important aspects to discuss in terms of successfully implementing a child perspective within adult mental health services. Prevention work is generally difficult, and so is implementation work.

Effective Strategies:

When we discuss preventive strategies and early intervention approaches, it is important to investigate what kind of evidence we have that prevention is effective. Durlak and colleagues conducted a meta-analysis in 1997, demonstrating that programs to prevent mental disorders can be effective for children.30 In 2002, Jané-Llopis found that effects of prevention programs are stable over time, and are effective for populations with different levels of risk.31 So generally there is evidence to support the use of preventive programs.

What about the programs specifically developed for the field of parental mental illness? Many of the strategies within preventive interventions involve aspects of parent training. The idea is that parent training programs can help families and children to regulate the child’s thoughts, feelings and behavior.32 Within the field of parenting there are several programs that have an extensive evidence base.33 Parenting programs may be used to promote good mental health in children also in the field of parental mental illness.34 Parent training programs is a good option for some of the families affected by parental mental illness, however depending on the diagnosis and the severity of the situation. Furthermore, these programs are used by a growing number of local communities, and may be easier to get access to than programs that are more specifically designed for parental mental illness issues.

There are also some programs that are more specifically designed to target families affected by parental mental illness. In 2012, a meta-analysis was published. The authors assessed the evidence in terms of effectiveness of the preventive interventions in decreasing the
risk of mental disorders in the offspring of mentally ill parents.

The conclusion in this meta-analysis is that the evidence indicated that such interventions may be effective and that different approaches to treatment of the families may be equally effective. However, the results from the studies reported in the meta-analysis mainly consisted of mothers with affective disorders and depression, and the results may therefore be less applicable to parents with other mental disorders and to fathers. Additionally, several studies included were of questionable standards and this may have led to an overestimate of the effects. The authors do however point to the need for further studies of sufficient size and high methodological quality.

In 2012, a review of intervention programs for children whose parents have a mental illness was published, providing an overview of available interventions. The authors of this review divided the interventions in three groups:

1. Family intervention programs.
2. Peer-support programs for children.
3. Online interventions for children/adolescents whose parents have a mental illness.

The most common component in the programs was provision of psychosocial education about mental illness. Only some of the interventions had been evaluated, and very few had been evaluated in Randomized Controlled Trials.

The authors concluded that more evaluations are needed in this field, and particularly studies that incorporate validated outcome measures.

So in the field of parental mental illness, what would be effective strategies for knowledge transfer? An effective strategy should take into account the fact that parental mental illness has serious consequences for children and that we can prevent the transgenerational transmission of mental illness by preventive interventions.

Furthermore, there are several existing interventions with good evidence of effect that can be used to train parents in better parenting strategies; e.g., the Incredible Years program or the PMTO (parent management training Oregon) intervention. There is a problem when policy makers and other agencies decide to disseminate programs that have no documented effects. In worst case scenarios, programs may prove to have negative effects. And, even if the situation should be that the strategy chosen had no effects—it would be a major waste of resources. This is why programs that have been evaluated and found to be effective should be priority number one, if such documentation exists. When planning effective strategies in this context, evidence based programs are preferable to interventions without evidence of effect. However, in order for a strategy to be effective, the implementation aspect has to be a part of the equation.

**Implementation of Effective Strategies:**

Knowledge transfer can be challenging and one perspective that may be useful in addressing these challenges is to be found in the substantial body of implementation literature. The essence of implementation is behavior change. Implementation is defined as a specified set of activities designed to put into practice an activity or program of known dimensions.

Currently, little is known about the processes required to effectively implement evidence-based programs on an international scale. Rigorous research to support the implementation activities that are being used is even scarcer. A major goal in the Implementation Research area is to help establish an evidence base for the implementation processes.

Implementation may involve different connotations for different people. When referring to implementation, different agents refer to a variety of contrasting activities and strategies; and the strategies they refer to represent varied depth and dedication. The differing views of implementation may be categorized as degrees of implementation in the following way. The first degree is paper implementation. This refers to putting new policies and procedures into place; e.g. legislation, commission documents and guidelines. However, changing policies and procedures does not change practice in itself.

The second degree is called Process implementation. This means incorporating new procedures into an organization; i.e. providing new guidelines and supervision, and changing reporting forms, among other things. However, the “mechanism” to change may not exist because this strategy does not incorporate any tools or specific intervention to guide the change in
behavior. The highest degree of implementation is commonly referred to as performance implementation. This is the most extensive degree of implementation, meaning that it provides content and tools to practitioners so that new procedures and processes have functional components for change. According to the implementation research literature, performance degree implementation strategies are more likely to be successful than the other two degrees of implementation.38

There are several core components that work together in any attempt to implement and sustain effective innovations.39 These core components are: decision support data system (for instance organizational fidelity measures), a facilitative administration that provides leadership and support in the process, system intervention to ensure the availability of financial, organizational and human resources, recruitment and selection, pre-service training, consultation and coaching, and finally staff performance evaluations. The integrated and compensatory nature of the core components embodies the perspective that organizations are dynamic, and there will be variations in the relative contributions of each component to the overall outcomes. However, if the core components are not taken into account and assessed in implementation projects, the result may be unsuccessful implementation processes.39 Even though there is some evidence to support the importance of the core components,39 more rigorous implementation research should be conducted to extend the evidence base of core implementation components.

Behavior Change:

Implementation of new routines involves behavior change. Many strongly believe that increasing knowledge and changing attitudes also change people's behavior. This is linked to a belief that awareness campaigns, education and a general focus on a subject, will cause behavior change in people. In the study of changing clinical practice to safeguard children of mentally ill parents, this view implies that information and courses for health professionals should have the potential to change clinical practice. Within health promotion campaigns, this has been a particularly common strategy,40 for instance campaigns to encourage people to stop smoking. The no-smoking strategy has been effective because the strategy has been multi-layered; from restricting the availability, banning smoking in public areas to strategies to change attitudes, and strategies to help people gain control over their behavior.

The point is: in order for a strategy to improve the situation for families affected with parental mental illness, the strategy must incorporate more than information about risk-factors. Behavior change is complicated. This implies that is not sufficient to simply point out why something should change, how the changes are to come about must also be determined. There is no reason to expect that positive general attitudes to improved services for children of mentally ill – or even increased knowledge about the risk of these children–automatically will change clinical practice. There is no theoretical or empirical foundation to expect specific skills and behaviors to arise from a general dissemination of knowledge and positive attitudes.

Where Should We Begin?

It is not of indifference where a process of knowledge transfer or behavior change should begin. A model which was developed by Maybery and Reupert in 2009 was designed as a hierarchy of points of intervention to affect workforce change, because it is unlikely that higher level activities can be successful unless the lower levels of the hierarchy already exists in the organization.41

The lowest level represents the importance of the policies within an organization, for example guidelines. Strategies to change practice have to be embedded in the organization, and the management has to be on board with the aims to change.

The next level of the hierarchy consists of issues relating to the workforce for example workers’ attitudes, skills and knowledge. The most important areas for workers to develop in this context include reporting systems, assessment, referral procedures and psychoeducation in regard to the service user. The groundwork of stage one and two will then enable the workers to engage with the service user.

Level three of the hierarchy represents the barriers families themselves bring in. Parents may not know the consequences their illness has on their children, or they may be reluctant to discuss this with others. Parents may have fears that discussing their insecurity and problems in childrearing may lead health personnel to worry about the quality of care their children receive, and consequently
that others will report them to the Child Protection authorities. Once organizational anchoring has been done and the workforce has been trained to engage with the clients in a family oriented perspective, only then is it realistic to achieve a clinical practice that incorporates the parental mental illness aspect.

You have to have the bottom levels first in order to achieve the top level. This means that in the process of changing clinical practice, one should always start with initial groundwork such as; creating a detailed protocol that accounts for time and resources within the organization, assessing organizational needs, addressing requirements from the health authorities and so on. According to the model, the resistance and unwillingness the service users may have to discuss their children will be less prevalent when organizational issues and workforce related problems have been addressed.

We did a slight modification of the model to adapt the model to a Norwegian context.\footnote{We believe that an infinite amount of resources and efforts at the lower level will not allow movement upwards, because the movement is hindered by a contextual dimension. We therefore added a contextual level to the model, to incorporate these challenges. The added dimension encompasses two important aspects that are external conditions, but with a potential large impact on the movement from one stage to the next in the model. The first aspect is (1) the organization of mental health care services, Services for adults and services for children are two very different organizations and not necessarily co-operating. The second aspect is (2) the geographical context in which the mental health care services are provided. Sometimes the home-community is very far away from the hospital the adult is admitted to. This makes it difficult, if not impossible, to bring in the children to visit and receive preventive interventions within adult mental health services. A possible solution to this could be to offer interventions in the local communities instead of the hospitals. However, since the workforce at the hospitals have better knowledge of the mental health issues of the parents; perhaps telecommunication solutions could be explored?} Indicators of Success:

Sometimes it is difficult to know for certain that the strategies chosen have been effective. What we think may be the case is not necessarily accurate. Clinicians or managers may have a hunch that what is done within the clinic to support children of mentally ill is good, based on perhaps one person’s very dedicated work in the area. It does not always mean that everyone is doing dedicated work. We need reliable ways of assessing success.

In terms of measuring success, we are talking about two different processes.

We’re talking about evaluating the effects of the interventions and in that sense monitoring if the strategy is successful (levels 3 and 4 in the hierarchy, Figure 1). We’re also talking about monitoring the implementation process and keeping an eye on the process of change at all times (levels 1 and 2 in the hierarchy, Figure 1).

Indicators of success in terms of client engagement and services for children and families (level 3 and 4, Figure 1) can be detected by studying the effects of the interventions. This implies that in terms of the interventions one chooses to apply in the field of parental mental illness, one way of measuring success is to look at the outcomes for children and families. To look for indicators of success you have to look into the evaluations on the intervention’s effect on parents and children, in efficacy studies, effectiveness studies or other approaches to evaluation. Good outcomes for children is in itself an indicator of a successful approach. Monitoring the outcomes for children is important in addition to monitoring the process of implementation of the intervention in real life. Fidelity is of course also very important. **In the field of program evaluation, the term fidelity denotes how closely a set of procedures were implemented as they were supposed to have been.** For example, it’s difficult to draw conclusions from a study about effective strategies in the field of parental mental illness if the practitioners are not able or willing to follow the procedures they received in training. Subsequently, higher fidelity is correlated with better outcomes, and therefore a significant factor in the assessment of success indicators. Studies that used fidelity scales have found better outcomes for consumers when services adhere closely to an approach with specified critical components and standards.\footnote{The other approach to measuring success is linked to studying the process of implementation, and documenting activities related to level 1 and 2 in the hierarchy (see Figure 1). In Implementation research – measuring processes of change is crucial in order to keep track of the progress of the change.}

The other approach to measuring success is linked to studying the process of implementation, and documenting activities related to level 1 and 2 in the hierarchy (see Figure 1). In Implementation research – measuring processes of change is crucial in order to keep track of the
indicators of success, and one aspect that is important to address is readiness to change. Organizational readiness to change is considered a critical precursor to achieve successful implementation of complex changes in healthcare settings. This implies that the implementation strategies should encompass activities to create motivation to change. On-going assessment of organizational readiness is very important in order to be successful in any attempts to change.

Furthermore, to keep track of the process it is important to evaluate the core variables that you want to change in the implementation strategy. In our study, these have been linked to knowledge, attitudes, collaborative routines and clinical practice related to families with parental mental illness. The road to success may not be as straightforward as we imagine when we set up our protocols and project plans, which is why we need to monitor the process. We need to be aware of what is going on along the way.

An example of a tool that can be used to monitor the process of change is measuring collective efficacy.

The term collective efficacy refers to individual group members’ perceptions of the capability of the group to achieve specific goals. In therapeutic organizations it represents the practitioners’ and the leaders’ perceptions as a whole that their agency is capable of creating positive outcomes for the children.

The readiness of an organization for successful implementation of evidence-based practices may be predicted in part by an organization’s level of collective efficacy. This means that a valid measure of collective efficacy in services may be particularly interesting in implementation research. However, as a self-report measure of capability to create positive outcomes for patients and families the tool is subjective and therefore limited. A solution to this limitation could be to include more concrete measures such as case load.

Sustainability:

If the implementation process is successful, and we have successfully transferred knowledge about parental mental illness and about effective interventions to
achieve the objectives of better outcomes for parents and children; how do we get it to stick? In terms of new-practice glue, the term to discuss is sustainability. Sustainability addresses the issue of how the new practice, the transferred knowledge, is to survive in the every-day practice.46

Finances are also a big issue, as many preventive interventions fail to become sustainable because insufficient resources are provided. Cost-benefit analyses play an important role in the planning and decision making process of implementation projects, and sustainability issues need to be a part of the analyses.

The goal with sustainability is the long term survival and continued effectiveness of the implementation site in the context of a changing world. A review article published in 2012 by Stirman and colleagues provides an overview of the current state of the research literature on the sustainment of interventions.46 One finding in this review was that partial sustainability was very common, meaning that elements of the implementation had survived, but not necessarily all elements that make up a program package.

The studies that reported on full sustainability were few and did not include long-term reports of post-implementation outcomes. Follow up measures to monitor sustainability is necessary and preferably more than just one-year follow up studies.

The conclusion was that the body of literature on sustainability was fragmented and underdeveloped.46 To advance what is known about sustainability will require time, resources and funding. Appropriate planning assessment and allocation of funds would result in much better understanding of why and how some interventions last and others do not.

There are of course a lot of challenges related to sustaining interventions in the field of practice. The sustainability strategies should encompass strategic support within the organization. The success and sustainability of evidence based practices can be substantially influenced by the quality of organizational support systems for the program and leadership support.

It is important to retain an ongoing capacity for sustaining the interventions.

Implementation projects need to be properly anchored in the organization. The management must actively support the implementation of a new practice, and this should be reflected in the policies within an organization, such as guidelines, service statements, protocols and interagency guidelines. Sufficient human resources and time to take on the new tasks must be allocated. Additionally, the managers must emphasize that the new practice is relevant and worth taking on. Otherwise, the hope of establishing the new routines within practice as usual is at risk. There must be ongoing recruitment of practitioners to carry out the interventions, which implies resource allocations. Sustaining interventions is reliant on core implementation personnel, but also on-going routine evaluations to monitor the implementation activities.

**Conclusion**

To sum up, where do we stand in general on knowledge transfer in the field of parental mental illness? We know something about effective strategies, we have well defined objectives, we have a few effective interventions, and especially interventions that target parenting behavior have a good evidence base. The evidence base on interventions specifically designed to address families affected by parental mental illness is growing, but more studies should be conducted in this area. We have models to help us understand behavior change and complex implementation issues. We even have ways to measure indicators of success, and we know something about how to create sustainable practices. The question is perhaps: do we have the patience? We need to recognize that knowledge transfer or implementation work is time consuming.

On the one hand; Researchers need to acknowledge the fact that they might have to work closer with the field of practice, and perhaps invest in longer time perspectives than traditional research projects. On the other hand; practitioners need to commit to the project protocols and invest time in adopting the new routines. If we pull together we can perhaps succeed in the endeavor to bridge the gap between research and practice.

Incorporating effective strategies in adult mental health services can potentially prevent parental mental illness being transmitted from one generation to the next. It is therefore important for both researchers and practitioners to remember why the extensive strategies to change clinical practice are important. For the children and families who may benefit from the changes, it may mean a world of difference.
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Hatherleigh's Note: Additional typeface treatment was added to text for emphasis. Supplementary title page information, CME, Best Practices, and medication trade names were also included.

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References


Multiple-Choice Questions

77. Which one of the following statements is correct regarding parental mental illness?
   A. Parental mental illness may interrupt the neurological development in offspring.
   B. Adults with mental health problems are not less likely to be parents than the rest of the population.
   C. Studies demonstrate that children of parents with mental illness are at risk of developing mental health problems themselves.
   D. All of the above.

78. According to the lesson, what does sustainability refer to in regard to parental mental illness?
   A. Sustainability denotes how closely set procedures are implemented as originally intended.
   B. Sustainability is the implementation of new routine.
   C. The goal of sustainability is the long-term survival and continued effectiveness of the implementation site in the context of a changing world.
   D. None of the above.
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Best Practices in CME

Knowledge Transfer in the Field of Parental Mental Illness: Objectives, Effective Strategies, Indicators of Success, and Sustainability

By Camilla Lauritzen, PhD; and Charlotte Reedtz, PhD

ID#: L003383

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Mental health problems are often transmitted from one generation to the next. However, transferring knowledge about interventions that reduce intergenerational transmission of disease to the field of parental mental illness has been very difficult. In this lesson, the authors discuss several aspects of knowledge transfer in the field of parental mental illness and a rationale for the importance of preventive strategies for children of mentally ill parents.

Key Point 1: Background of Parental Mental Illness

Parental mental illness is considered a powerful risk-factor, with a potential of serious impact for the children.

Key Point 2: Sequelae of Parental Mental Illness in Children

Parental mental illness present during the early years of children’s lives can trigger dysregulated emotional patterns, negative emotionality, and insecure attachment. Developmental traumas tend to manifest in several disorders such as regulatory disorder during infancy, attachment disorders, hyperkinetic conduct disorder at school, or combined conduct and emotional disorders during adolescence.

Key Point 3: Prevention of Mental Illness and Protective Factors

Helping children of parents with mental illness achieve self-regulatory competence is essential. Strengthening protective factors, (i.e., family related factors, individual factors, and structural factors) in these children will help mitigate the development of mental illness.

Key Point 4: Implementation of Strategies

The transfer of knowledge to address the challenges in preventing parental mental illness from being passed to children key. Studies indicate the need for further research to ascertain whether promising results consisting of mothers with affective disorders and depression can be applied to parents with other mental disorders and fathers. Nonetheless, family intervention programs, peer-support programs for children, and online intervention for children/adolescents whose parents have a mental illness are effective.

Key Point 5: Sustainability is Key

Once clinicians and policy makers decide upon a treatment program, not only is implementation key, but sustainability—which addresses how the new practice, and
the transferred knowledge is to survive and be maintained in daily practice, is essential. The goal of sustainability is the long-term survival and continued effectiveness of the implementation site in the context of a changing world.