



## SEEG

Examining Decision-making in Epilepsy Patients:  
Using Stereoelectroencephalography to Unravel  
Pathophysiological Mechanisms in Psychiatry

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# Psychiatry Insights 2014

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## Dear Colleagues,



Welcome to another edition of *Psychiatry Insights*. This publication represents issues relevant to our field that are being addressed at Cleveland Clinic. I trust you will find it worthwhile reading and that the contents will be a catalyst for dialogue and collaboration.

We are all well aware of the grim recent nationwide surge in heroin addiction and the accompanying rise in overdose fatalities. This drug abuse epidemic is the sixth in this country's recent history, according to my colleague Gregory Collins, MD, the Section Head and founder of Cleveland Clinic's Alcohol and Drug Recovery Center. For Dr. Collins, the wave of heroin cases must bring about a profound sense of *déjà vu*. His career in addiction medicine began in the U.S. Navy during the Vietnam War, when opiate addiction was a significant problem among returning servicemen and the nation at large.

Helping patients break the grip of drug dependence is a crucial part of our responsibility as behavioral health physicians. But as Dr. Collins notes in his article, an effective response to the epidemic requires collective as well as individual action.

Cleveland Clinic is now part of a comprehensive effort in Ohio to combat heroin addiction through a collaboration among physicians, legislators, law enforcement officials, educators and others. It's a reminder that behavioral health innovation today comes not only through hard science and clinical initiative, but also via social and political means. At Cleveland Clinic's Center for Behavioral Health, we strive to be involved in all those areas.

Also in this issue, Amit Anand, MD, writes of his efforts to determine if dysregulated gene expression is at the heart of bipolar disorder's dramatic mood swings. Tatiana Falcone, MD, details her search for biomarkers that may reveal a physical harm — a breach in the blood-brain barrier — related to childhood emotional trauma. Adele C. Viguera, MD, MPH, reveals worrisome levels of suicidal ideation in multiple sclerosis and epilepsy patients and the need for interventional screening.

Neuroscientist John T. Gale, PhD, and neurosurgeon Jorge Gonzalez-Martinez, MD, PhD, describe their novel use of stereoelectroencephalography and a simple card game to probe cognition and better understand the link between brain function and behavior. Their results are preliminary but provocative.

Several of our authors explain the valuable, team-oriented role that behavioral health specialists can play in treating pediatric chronic pain, managing bariatric surgery patients and providing palliative care.

Finally, David W. Streem, MD, underscores the importance of applying outcomes measurement to behavioral healthcare, a major focus for us here at Cleveland Clinic.

Thank you for taking time to read *Psychiatry Insights*. Please feel free to let us know what you think. We'd love to hear from you.

Sincerely,

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# Examining Decision-making in Epilepsy Patients: Using SEEG to Unravel Pathophysiological Mechanisms in Psychiatry

By John T. Gale, PhD, and Jorge Gonzalez-Martinez, MD, PhD



John T. Gale, PhD



Jorge Gonzalez-Martinez, MD, PhD

The neural mechanisms that underlie psychiatric disorders are difficult to understand, due to the lack of animal models that adequately represent psychiatric disease states and limitations in the investigational tools available to study human populations.

Cleveland Clinic's Department of Psychiatry and the Epilepsy Center have recently undertaken a series of behavioral and electrophysiological experiments in patients undergoing evaluation of their seizure disorder. The aim of these experiments is to directly measure the neural control of cognitive processes using an invasive electrophysiological method known as stereoelectroencephalography (SEEG) that can simultaneously record electrical activity from many parts of the brain at high temporal resolution (~1 ms).

These experiments are expected to provide significant insight into mechanisms that underlie psychiatric disease. They avoid using animal experiments that are difficult to interpret and instead employ leading-edge electrophysiological methods for assessing brain function.

## Using SEEG to Localize Epileptic Activity

In these seizure disorder patients, many SEEG electrode contacts (as many as 200) are placed directly into the brain to define the area responsible for disease. This methodology has been pioneered in the United States by one of us (Dr. Gonzalez-Martinez) and uses advanced imaging methods in coordination with stereotactic tech-

niques to precisely map the cortical areas responsible for generation and propagation of epileptic activity.

The SEEG method involves rigorous preimplantation scrutiny of all available findings from the noninvasive phase to define the likely location of the epileptogenic zone. The implantation strategy is based on the respective weight of MRI, interictal/ictal EEG and ictal clinical characteristics, which may vary greatly from patient to patient.

After formulating an individualized hypothesis about the epileptogenic zone's location, physicians plan a tailored SEEG implantation strategy with the goal of confirming or rejecting the hypothesis. The precision of the stereotactic technique allows the desired targets to be reached and recorded from lateral, intermediate or deep structures in a three-dimensional arrangement, thus accounting for the dynamic, multidirectional spatiotemporal organization of the ictal discharges (Figure 1).

## A Research Opportunity to Probe Cognition

Once these contacts are positioned, patients remain in the hospital for as long as three weeks. During this time, we can have patients perform a battery of behavioral tasks designed to probe various aspects of cognition.

While the goal of the SEEG implantation is to define the patients' seizure disorder, these patients often welcome the opportunity to participate in our research, as it provides them with some level of distraction during their hospitalization. Moreover, this research does not pose additional risk to patients and can be performed in the hospital room, without interfering with the clinical analysis of their epilepsy. Prior to participation, subjects review a consent form outlining the study's goals and potential risks. The research has been approved by Cleveland Clinic's Institutional Review Board.

Here we present the results of a behavioral task used to probe the processes of decision-making and reward encoding, two fundamental brain functions thought to

### KEY POINTS

Understanding neural mechanisms that underlie psychiatric disorders is difficult due to inadequacy of animal models and limitations of investigational tools.

Stereoelectroencephalography (SEEG), currently used to identify the epileptogenic zone in seizure disorder patients' brains, also can be utilized to record neural activity during various cognitive tasks.

We are using SEEG to probe the processes of decision-making and reward encoding, two brain functions that may be involved in major depression and obsessive compulsive disorders.

be involved in major depression and obsessive compulsive disorders. In this task, patients play a card game against a computer while their brain activity is recorded.

The card game is similar to the child's game of War. Patients are required to make a financial wager based on their expectation of beating the computer's card. To make the game simpler for analysis, we limit the cards to even-numbered ones of the same suit (e.g., 2, 4, 6, 8 and 10 of spades). Thus, the 10 card represents the highest odds of winning and the 2 card the lowest, with the 6 card representing a 50 percent chance of winning.

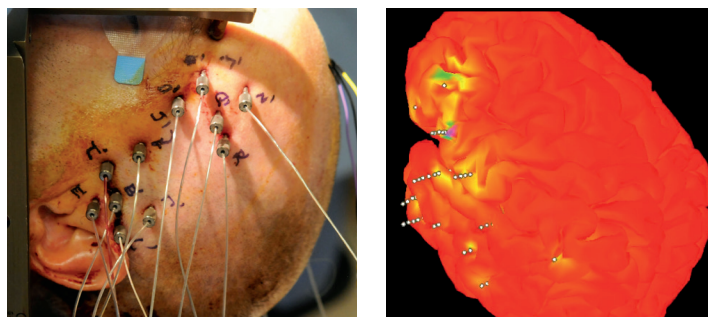
The patient first sees his or her card and the back of the computer's card. After a brief delay, the patient is asked to make a wager of either \$5 or \$20, based on the expectation of winning. The patient then is shown the computer's card, followed by a screen depicting whether the patient's hand wins or loses.

#### Differing Choices Elicit Differing Neural Patterns

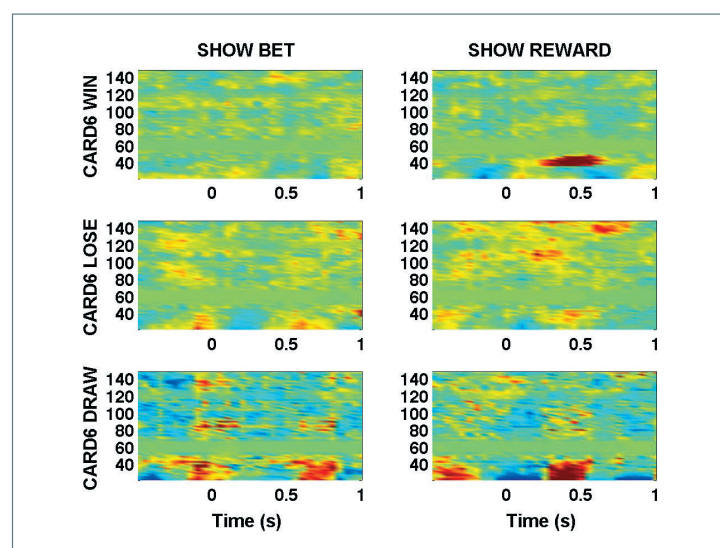
In a precursory analysis of the SEEG data capture from one patient playing the game, we can demonstrate that various aspects of the task evoke significant gamma-band modulation in the brain. In the visual cortex, the presentation of an object on the screen results in a fast-latency (~200 ms) response, regardless of task outcome. In contrast, the inferior frontal gyrus is modulated only in trials that result in a reward (Figure 2). This modulation is longer in latency (~300 ms), suggesting a period when the reward information is being processed. The reward-related responsiveness is consistent with the function of that part of the cortex, as it is hypothesized that the inferior frontal gyrus is involved in decision-making and reward evaluation.

Although preliminary, these data are exciting because they demonstrate that the behavioral task elicits different responses in the brain that are dependent on the patient's choice.

Functional magnetic resonance imaging has been used to study neural firing patterns during behavioral tasks, but it can resolve global fluctuations only in response to the overall task. The SEEG method is capable of resolving brain activities at scales relevant to the behavior being studied, allowing us to see brain fluctuations related to



**Figure 1.** Patient in stereotactic frame with SEEG recording electrodes in place (left); three-dimensional model (right) shows brain region activation during phases of the card game. The 3-D image was constructed with Brainstorm Image reconstruction software. (See: Tadel F et al. Brainstorm: A User-friendly Application for MEG/EEG Analysis. Comput Intell Neurosci vol 2011; Epub 2011 Apr 13.)



**Figure 2.** Spectrograms of activity in the inferior frontal gyrus relative to two different epochs ( $t = 0$ ) in War task. (X axis: Time relative to epoch. Y axis: Frequency. Color represents z-score relative to baseline.)

individual time periods of the task, such as when patients see their card or the outcome of their bet.

Our next goal is to extend our analysis across many more brain regions in patients that we have recorded, to gather a larger picture of how the brain governs decision-making. In the long term, we plan to apply this knowledge to better understand how changes in these parts of the brain contribute to psychiatric disease, and to develop new strategies for treatment. ■

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## A Call to Arms to Combat the Epidemic of Heroin Addiction

By Gregory Collins, MD



Gregory Collins, MD

During my 40 years in medicine, America has endured approximately five drug epidemics, from LSD in the 1960s to crack cocaine in the 1980s. None of the previous epidemics compares to today's horrendous plague of prescription drug abuse and heroin addiction.

This epidemic is killing far more people than its predecessors. Fueled by powerful opioid drugs and cheap heroin, the rate of drug overdose deaths has tripled since 1990. Drug overdoses have become the leading cause of injury death in the United States, killing more than 38,000 people in 2010, according to the Centers for Disease Control and Prevention. Pharmaceuticals, predominantly prescription drugs, caused most of those deaths.

### Large Increases in Overdose Deaths

Opioid addiction and its tragic consequences touch every facet of every community, from the central city to suburbs, rural towns and small villages. In Cuyahoga County, home of Cleveland Clinic, 195 people died from heroin overdoses in 2013, according to the county medical examiner. That is a 21 percent increase from the previous year and nearly five times the number of heroin overdose deaths that occurred in Cuyahoga County in 2007. Other major metropolitan areas have seen similar rises.

This is a full-blown public health crisis. The time has come for the medical community to acknowledge that it should be part of the solution.

Physicians who prescribe opioids are increasingly aware of the risks and problems of using these powerful drugs. We have come through a period in which aggressive treatment of pain was the norm. Now, we have a much more cautious mindset. Physicians and patients alike are coming to the realization that minor pain should be treated first with nonsteroidal anti-inflammatory drugs or similar nonopioid medications.

(In Cleveland Clinic's Department of Pain Management, the role of opioids in treating chronic pain is very small and limited to a narrow subset of patients, mostly those with cancer. Also, any plan to start a patient on opioids must include a plan to monitor their effect using specific outcome measures and to stop their use if defined treatment goals aren't met.)

People addicted to painkillers have helped drive demand for heroin. Addicts turn to heroin because it is cheaper than prescription drugs and in many cases is easier to obtain. Heroin also has lost its reputation as a drug to be feared. It has become fashionable and seems less risky. First-time heroin users often believe they can smoke it rather than resorting to a needle. When they become addicted, smoking quickly gives way to injection, with a heightened risk of overdose and death.

In my position as an addiction psychiatrist, I often ask our young opiate patients, whose average age is 22, if they have ever experienced cardiac or respiratory arrest and had to be resuscitated. Most say yes.

They also say many of their friends are already dead from overdoses.

### Responding to the Crisis

These dreadful things don't have to happen. But to curb an epidemic that grows like cancer, we must answer the call to action. Cleveland Clinic has decisively stepped up to address this public health crisis.

Two years ago, Toby Cosgrove, MD, CEO and President of Cleveland Clinic, hosted our region's first Drug Enforcement Summit, in collaboration with Steven M. Dettelbach, U.S. Attorney for the Northern District of Ohio. The second summit, in November 2013, drew more than 1,000 people and produced a community action plan that deals with prevention and education, healthcare policy, law enforcement and treatment. This broad-based community initiative is drawing national attention as a model for responding to the problem of rampant drug abuse.

One outgrowth of this initiative is a growing understanding that we cannot arrest or treat our way out of the problem. But we can follow national recommendations. They include increasing public education about abuse, addiction and overdose deaths. We need a strong educational thrust in middle schools, high schools, colleges

and medical schools. Laws and regulations governing the prescribing and dispensing of opioids should be tightened. Drop boxes should be made available at police stations for the secure disposal of unneeded or excess prescription pain medications, to get them out of circulation. We need more addiction treatment availability and capacity, from inpatient detoxification facilities to outpatient management with medication and counseling.

Cleveland Clinic provides stepwise treatment that matches individual patient needs, including detox therapy for outpatients, counseling, toxicology testing and medication assistance as needed, along with traditional 12-step approaches.

### Buprenorphine and Naloxone

Medication-assisted treatment with buprenorphine has revolutionized anti-addiction therapy, producing impressive outcomes. Our addiction research at Cleveland Clinic is finding that about three-fourths of heavily dependent opioid users respond well on buprenorphine. Our comprehensive treatment approach, including buprenorphine use, often helps patients break their addiction and gain a new lease on life.

We also need laws such as one passed recently in Ohio that improve the availability of naloxone for emergency use by addicts, family members and first responders. Naloxone reverses overdoses instantly, saving lives that otherwise would be lost. Public education is needed so bystanders know that an overdose is a critical emergency. In several places, Good Samaritan laws are being enacted to protect bystanders who report drug overdoses.

Most states now have prescription-monitoring programs that have become very effective at identifying drug abusers and doctor-shoppers. Physicians who treat pain patients with opioids should be trained to routinely use these monitoring programs as part of their practice.

The abuse of controlled medications is a national emergency. The casualties from this epidemic will soon exceed all the losses from the Vietnam War, with no signs of abating.

Our summit meetings in Northeast Ohio have shown that the medical community is ready to work with lawmakers,



law enforcement personnel and the courts to combat the misuse of prescription drugs and the spread of heroin.

Here in Ohio we are creating a national model for responding to this epidemic. If we use our collective brainpower, we can reduce the spread of addiction and save lives. We can prevent more parents from getting a call in the night that their child was found dead with a needle in his or her arm. ■

**Dr. Collins** is Section Head of Cleveland Clinic's Alcohol and Drug Recovery Center, which he founded in 1980. He also chairs the Health Policy Committee of U.S. Attorney for the Northern District of Ohio Steven M. Dettelbach's Heroin and Opioid Task Force. He can be reached at [colling@ccf.org](mailto:colling@ccf.org) or 216.363.2347.

### KEY POINTS

Heroin addiction is a tragic and growing national problem.

This public health crisis requires a broad-based community action plan that involves increased prevention and education efforts, changes in healthcare policy, stricter laws and regulations governing the prescribing and dispensing of opioids, and greater treatment availability and capacity.

# Measuring Behavioral Health Outcomes: Proper Attitudes, Appropriate Benchmarks and Efficient Data Collection Are Vital

By David W. Stroom, MD



David W. Stroom, MD

**What do you need to implement a world-class outcomes measurement and quality improvement program?**

Many providers, especially those in behavioral healthcare, may find the prospect of measuring outcomes intimidating, even frightening. We often pride ourselves on knowing our patients better than do other providers, and we may feel that measuring outcomes is unnecessary because our patients feel so familiar to us. We may think that if our patients are not doing well, we would have a strong sense of this without having to collect and analyze data. We all feel well-trained and knowledgeable about the latest techniques.

But unless we have the opportunity to prove to ourselves, our patients and the public that our efforts produce the desired effects, we are working with untested theories and the value of our work cannot be determined.

In the future, demonstrating the value of the healthcare we provide will be an inescapable reality. While published studies for decades have analyzed the financial impact of screening tools and therapies, there now are tools that can assist the individual provider or small group in examining the effects of their efforts. Before any of these tools can be implemented, however, the provider must ensure that some simple traits are in place. Without the following three principles firmly established in our minds, any quality improvement effort will be threatened as soon as difficulty appears.

## Humility

The great organization must be a humble organization. The great professional must be a humble professional. We must always accept that we are not perfect and can do better. When we believe we are already as effective as we can be, innovation and quality improvement stops, because it must not be necessary.

As mental health professionals, we have close relationships with our patients, and those relationships last a long time. Many of these patients are very grateful for the support and guidance we provide. While these expressions of loyalty and gratitude can be satisfying, they also can distort our professional perceptions.

To be as effective as possible for the next patient we meet, we must perceive the effect of our involvement with patients as clearly as we are able, for good or ill. If we are truly humble, we are not concerned that our initial outcome measures may not turn out the way we hope,

## KEY POINTS

Identify an appropriate outcome measure for a particular patient population in the practice.

Identify a nationally accepted or otherwise relevant benchmark for comparison.

Make data collection efficient (and automated, if possible) to facilitate outcomes reporting and quality improvement.

Identify targeted areas for improvement and design an intervention to address the needed improvements

because we already accept that we are imperfect. Instead of being concerned, we must feel excited that we have found an opportunity to improve.

## Curiosity

As behavioral health professionals, we tend to be curious about our patients — their backgrounds, history, and why they chose this particular time to seek help from this particular provider. We should be equally curious about how to reliably measure improvement in our patients or how we might emulate others' efforts in our field. If we are humble and curious, we want to know if our outcomes are as good as those of our colleagues and, if not, why not. Some variables that affect outcome are controllable; others are not. But often with enough curiosity and creativity, we can find ways to control the controllable aspects of our work.



## Courage

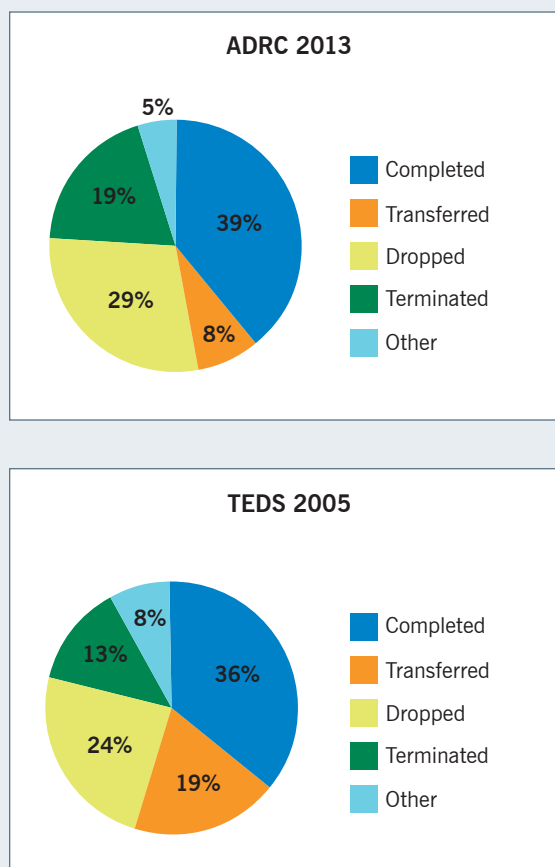
If we look at the effectiveness of our own care, we will inevitably learn things that do not comport with our experience or training, or the advice of our mentors. We must then have the courage to change. We must be willing to change how we work and with whom we work. Success may not come on our first attempt. A number of changes may be required to see the impact we hope for. But we must have the courage to question our beliefs about our work. The future demands it. So do our patients and those others who are paying for our services. And we should demand it as well.

Once these principles are established, often data collection becomes the greatest hurdle to overcome. Creating efficient ways of collecting data (either by patient self-reporting or entered by providers) permits rapid accumulation of information for analysis while posing a minimal burden.

## The Knowledge Program

Cleveland Clinic's Center for Behavioral Health has worked with the Neurological Institute to develop the Knowledge Program, now part of Cleveland Clinic's Clinical Systems Office. The intent of the Knowledge Program is to create a system that allows patients and caregivers to enter data for analysis of outcomes and quality improvement, research, and administration. The program permits data entry at the time of appointment, but patients can also access the system from their home computers and other platforms so that feedback can be received when it is more convenient, thereby improving compliance and the reliability of the data collected.

The Knowledge Program interfaces with the larger electronic medical record. The modern electronic medical record is so much more than a means to document encounters. It gives us the opportunity to collect, analyze and report data efficiently. In addition, a sophisticated, customizable electronic medical record system can reduce unnecessary variations in care and aid in teaching trainees and new hires. It can facilitate coding and reimbursement and reduce legal liability. ■



**Figure 1.** Outcomes from Cleveland Clinic's Alcohol and Drug Recovery Center (ADRC) partial hospitalization and intensive outpatient programs from July 1, 2013, through December 31, 2013, are compared with national figures across 32 states from the Treatment Episode Data Set (TEDS), most recently reported in 2005.

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## SUGGESTED READING

Cosgrove, T (2014). *The Cleveland Clinic Way*. New York: McGraw Hill.

## Lymphocyte Gene Expression Differences Between Bipolar Mania and Depression

By Amit Anand, MD



Amit Anand, MD

Bipolar disorder is a serious emotional disorder marked by periods of depression and manic and normal (euthymia) moods. Despite decades of research, the biological basis for these changes is still unclear. Changes in brain circuitry oscillations, neurochemical changes and even switching on and off of genes have been proposed.

The latter hypothesis regarding dysregulated genes is particularly intriguing, as bipolar disorder has a strong genetic basis. Moreover, changes of gene expression have been shown to be related to circadian and seasonal rhythms. Therefore, dysregulated gene expression may underlie the different mood phases seen in bipolar disorder.

To test this hypothesis, we conducted a study in which genomewide gene expressions were measured in peripheral blood cells for 24 bipolar disorder patients. It has been demonstrated that gene expression in peripheral blood lymphocytes is reasonably well-correlated with expression in the central nervous system.

We collected samples from depressed and manic bipolar patients and analyzed them for RNA (gene expression) using the Affymetrix GeneChip® Human Gene 1.0 ST Array. Gene set enrichment analysis (GSEA) was con-

ducted to identify pathways that are dysregulated in patients. KEGG Pathway and Biological Process Gene Ontology (BP: GO) Pathway (downloaded from the Broad Institute's Molecular Signatures Database) were additionally used for pathway analysis.

Genomewide gene expression profiles were generated for manic (N = 12) and depressed (N = 12) subjects and resulted in gene expression data for 20,093 genes. Manic and depressed subjects were compared using one-way analysis of variance.

### Genes in Manic and Depressive Patients Have Differing Expression

Results for the 10 most significant genes and 10 most significant pathways from GSEA are shown in Tables 1 and 2.

**Table 1. Top 10 Genes with Differences Between Mania and Depression**

Gene	p value	Function	Associated Pathway	Associated Disease
KDM4A	0.00004	Protein coding		Wiskott-Aldrich syndrome and Kaposi sarcoma
CENPO	0.00006	Protein coding	Mitotic anaphase and prometaphase	Type 1 diabetes
PIK3R6	0.0001	Protein coding		
DIAPH3	0.0001	Protein coding	ERK signaling and regulation of actin cytoskeleton	Auditory neuropathy and benign epilepsy with centrotemporal spikes
P2RX3	0.0002	Protein coding	CREB pathway and class A/1 (rhodopsin-like receptors)	Burning mouth syndrome and cystitis
PRAME	0.0002	Protein coding		Acute leukemia and melanoma
GRLF1	0.0002	Protein coding	Regulation of actin cytoskeleton and axon guidance	Colon cancer and retinitis
ANKRD52	0.0002	Protein coding		
ACTL7A	0.0004	Protein coding		Riley-Day syndrome and dysautonomia
NLRP4	0.0004	Protein coding	Immune system and cytosolic DNA-sensing	Crohn disease and chronic lymphocytic leukemia

In the comparison of gene expression in peripheral lymphocytes between manic and depressive patients, a number of genes had significantly different expression. As seen in Table 1, most of the genes were protein coding, and one involved in signal transduction (phosphoinositide-3-kinase) was among the top 10 significantly different genes.

On examination of the functions of these genes from the GeneCards® database and from the data available from the top 10 pathways recognized to be different between mania and depression, it appeared that genes involved in cell division and the cellular cytoskeleton were the most different between the two groups. This is a novel molecular finding regarding differences between the neurobiology of depression and mania.

Another interesting finding was that many of the genes identified were associated with neurological illnesses such as neuropathy, epilepsy and dysautonomia, while others were associated with different types of cancers.

### Discussion and Future Research Directions

At this time, we can only speculate on the implications of these findings. Recent research has shown that cell division is closely linked to circadian rhythms and that molecular mechanisms of circadian rhythms provide information regarding changes in other cellular metabolic processes (Hong et al, 2014).

Hence, genes involved in cell division may also be involved in or influence hormonal or metabolic processes that determine circadian rhythms (Panda et al, 2002). Therefore, the dysregulated genes that relate to cell division will need to be studied in terms of their relationship to circadian rhythms. Gene expression will also need to be measured in the same patients when they switch from one mood to the other to investigate whether the genes identified may be involved in mood switching.

It has also been shown that many cancer cells become autonomous and are not influenced by circadian rhythms, as normal cells are (Fu et al, 2002). The relationship of some of the genes identified in this study to some forms of cancer may therefore be an indicator of disruption of circadian rhythm molecular mechanisms involved in the pathophysiology of bipolar disorder. ■

**Table 2. Top 10 Genetic Pathways with Differences Between Mania and Depression. GSEA = gene set enrichment analysis**

Pathway	GSEA p value
PURINE_RIBONUCLEOTIDE_METABOLIC_PROCESS	< 0.001
KEGG_MISMATCH_REPAIR	< 0.001
KEGG_NON_HOMOLOGOUS_END_JOINING	< 0.001
RIBONUCLEOTIDE_METABOLIC_PROCESS	< 0.001
NUCLEOCYTOPLASMIC_TRANSPORT	0.002
KEGG_DNA_REPLICATION	0.002
NUCLEAR_TRANSPORT	0.004
REGULATION_OF_INTRACELLULAR_TRANSPORT	0.004
KEGG_SELENOAMINO_ACID_METABOLISM	0.008
KEGG_O_GLYCAN_BIOSYNTHESIS	0.008

### KEY POINTS

Dysregulated gene expression, and particularly expression changes related to circadian and seasonal rhythms, may underlie the different mood phases seen in bipolar disorder.

A comparison of gene expression in peripheral lymphocytes between bipolar patients with mania and depression found that a number of genes have significantly different expression.

Genes involved in cell division and the cellular cytoskeleton appear to be the most different between the two groups.

Cell division is closely linked to circadian rhythms, so the dysregulated genes related to cell division should be studied in terms of their relationship to circadian rhythms and their possible involvement in bipolar mood switching.

**Dr. Anand** is Vice Chair for Research at Cleveland Clinic's Center for Behavioral Health and directs the Mood and Emotional Disorders Across the Life Span (MEDALS) program. He is a Professor of Medicine at Cleveland Clinic Lerner College of Medicine. Dr. Anand can be reached at [ananda@ccf.org](mailto:ananda@ccf.org) or 216.636.2840.



# Chronic Pain and Associated Depression/Anxiety in Children: A Treatment Strategy

By Veena Ahuja, MD



Veena Ahuja, MD

Cleveland Clinic Children's Pediatric Pain Rehabilitation Program works to bring children and adolescents out of a world controlled by pain and enable them to be happy, healthy and functioning. The addition of psychiatry into these types of medical programs can round out a well-balanced approach to physical and mental health.

Some physicians may be surprised to learn that children and adolescents frequently suffer with chronic pain. Various studies estimate the prevalence rate of persistent pain in this age group at between 15 and 32 percent. Its origin may be physical trauma, a disease or disability, or surgery or another medical procedure.

Children most commonly describe chronic pain as headaches or abdominal pain; other common types of chronic pain include limb pain, back/spine pain, fibromyalgia and combined pain syndromes (where more than one type of pain is present).

Prevalence of chronic pain disorders increases with age and may complicate an already difficult period of development for a young patient.

## Depression Complicates Chronic Pain Remission

The addition of depression and/or anxiety can make it nearly impossible for a child to achieve remission from pain. Certain factors affect the likelihood of a healthy adaptation to a medical diagnosis. Specifically, an unpredictable disease course and prognosis, strong stigma associated with a disorder, and a high level of monitoring

required by the family are all factors that impede a patient's psychological adjustment to an illness.

Furthermore, dealing with a child or teen with chronic pain can alter a family's ability to function normally, especially if the patient is no longer able to attend school, participate in family activities, and/or continue his or her extracurricular activities.

Because most patients with these disorders are informed that their pain is likely to resolve with specific medical treatments, there is a strong drive to request more diagnostic procedures to find the elusive diagnosis that will lead to an effective treatment and miraculous recovery.

Chronic pain is an "invisible" disease that often leaves no physical mark, leading to significant skepticism and, oftentimes, bullying by peers who may feel the patient is "faking it."

Finally, the constant, daily fight to manage medical symptoms and prevent future pain crises can be exhausting. All in all, it is no surprise that chronic pain can be both a precipitating factor and a perpetuating factor of depressive and anxiety disorders.

## The Difficulty of Mental Health Referral

Approaching a chronic pain patient as a psychiatrist can be a tricky business. Families and patients often regard referrals to psychiatry and psychology as a sign that they are not being taken seriously. Many patients are sensitive to others' perceptions that their pain isn't "real"; therefore, a mental health referral indicates "it's all in my head."

Many of these patients have grudgingly agreed to psychiatric evaluations in the past in hopes that their primary physician will approve more medical treatments.

Caregivers in our Pediatric Pain Rehabilitation Program help families move past diagnostic studies and invasive treatments, to focus on function and returning to an enjoyable life.

### KEY POINTS

Children and adolescents frequently suffer with chronic pain. The addition of depression and/or anxiety can complicate achieving remission.

The addition of psychiatric care to a pediatric pain rehabilitation program can help address the interconnectedness of chronic pain and depression.

Treatment may include providing individual and group psychotherapy, teaching problem-solving skills, addressing insomnia and administering antidepressant medications.

Patients are expected to keep a regular sleep schedule, to work hard not only at physical and occupational therapy but also at individual and group psychotherapy, and, most of all, to develop and apply problem-solving skills as a way to return to a more normal life.

Problem-solving may start with motivational interviewing techniques to improve adherence to a plan, followed by clearly defining the issue, brainstorming possible solutions, evaluating what the patient is willing to do and, finally, determining the best next step that all parties agree to. Patients are discharged with clear goals, including restarting pleasurable activities.

The diagnosis of psychiatric disorders and use of psychotropic medications is not a way of dismissing patients' very real and debilitating pain disorders; instead, we present it as a way of smoothing their transition back to full-time school and activities.

### Chronic Pain and Depression Are Interconnected

When we evaluate the true effect pain has had on an adolescent's life, we encounter missed opportunities, broken relationships and, most of all, a loneliness that comes from being left out at a time when being with peers takes on the utmost importance. As many teenagers struggle to see beyond their current frustration, they describe worries that they will live the rest of their lives dragged down by pain.

The physical symptoms that accompany pain often mimic those of depression and anxiety (poor sleep, poor focus, appetite changes and decreased interest in activities that used to be pleasurable). Chronic pain patients struggling with depression and anxiety are unable to escape these symptoms, even when pain has temporarily abated. As with the often described "sick role," being a patient with pain becomes a part of each patient's personality.

Fortunately, there is hope. The Pediatric Pain Rehabilitation Program helps patients move past their pain diagnosis and utilize their strengths and resources to return to a more active, fulfilling life.

A vital piece of this return to functioning includes adequate treatment of any psychiatric disorders that are present, to give a patient the best chance of recovery.



While these evaluations are not required as a part of the pain program, they are often recommended based on team consensus and/or parent request. Evaluations include interviews with patient and family, a review of the patient's medical records, and input and observations from the rehabilitation team.

### Post-discharge Care Is Important

Recommendations for patients with anxiety or depressive disorders always include instructions to continue individual psychotherapy following discharge from the program. For patients with primary anxiety or depressive disorders, selective serotonin reuptake inhibitors continue to be the first-line treatment; for many patients with a combination of depression and pain syndromes, selective norepinephrine reuptake inhibitors, such as duloxetine, can be used with careful monitoring for activation.

For chronic pain patients with insomnia, sleep hygiene is strongly encouraged. Over-the-counter melatonin and/or medications such as trazodone may also be helpful.

As our knowledge of the interplay between pediatric pain and mental health disorders continues to expand, we have increasingly more interventions to offer these patients. By breaking down the stigma surrounding psychiatric and pain disorders, clinicians can help patients and their families adapt to and move beyond their medical conditions to a life well lived. ■

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## Palliative Medicine and Psychiatry: A Natural Alliance

By Harold Goforth, MD



Harold Goforth, MD

Palliative medicine is the medical subspecialty that specializes in quality of life and symptom management for those with serious and life-limiting disease. It can be reached through multiple and diverse primary specialty boards, including internal medicine, family medicine, surgery and psychiatry, among others.

Psychiatry is the branch of medicine that specializes in the management of mental illness and general medical diagnoses with psychiatric or behavioral manifestations.

While on the surface the two specialties may seem worlds apart, they actually share a great deal of subject matter. For instance, psychiatry has long maintained a subspecialty in geriatrics that focuses on diseases of the aged. Many of those geriatric conditions are primary diagnoses that palliative medicine also addresses (e.g., dementias) or are consequences of aging and the end of life (bereavement).

This article seeks to demonstrate the overlap of the two specialties and how psychiatry intersects with and contributes to the interdisciplinary nature of palliative medicine. Certainly, both fields value a multidisciplinary approach, with excellent communication skills necessary to the trade.

### Shared Appreciation of the Interdisciplinary Team's Value

One of the determining characteristics of palliative medicine is attention to an interdisciplinary team to evaluate, diagnose and treat the individual. Palliative medicine relies on a biopsychosocial assessment, as does psychiatry, and utilizes supportive medical fields such as nursing, social work, art therapy, chaplaincy, physical therapy and nutrition. It seeks a holistic appreciation of the individual patient, to better help one attain his or her particular goals. The palliative medicine physician is the leader of this interdisciplinary team and coordinates the overall multidisciplinary assessment.

While participation in an interdisciplinary team may be a novel experience for some in medicine, psychiatrists are taught these management and collaborative skills from early in their residency in the assessment of psychiatric illness. Similarly, adopting a biopsychosocial model has long been the standard of care for psychiatric assess-

### KEY POINTS

Though seemingly dissimilar, palliative medicine and psychiatry have a surprisingly large overlap in terms of approach, skills and treatment experiences.

An appreciation of these commonalities is beneficial to both specialties and can lead to improved patient care.

ment and treatment. Thus, from an overall treatment approach, there is much overlap in the holistic orientation that both palliative medicine and psychiatry use to characterize and better understand their patients.

There is considerable overlap with the two specialties at a more granular level as well. Diagnostically, psychiatrists have long been at the forefront of treating patients with serious and life-limiting illnesses such as dementia and other neurodegenerative disorders — treating them from a cognitive standpoint as well as for the behavioral complications that accompany these diagnoses. In advanced stages of the dementing disorders and associated diagnoses such as Huntington disease, it is common for psychiatrists to treat patients until the time of death. In fact, almost every life-limiting neurological and psychiatric diagnosis comes with profound behavioral alterations; psychiatry routinely assesses and participates in the treatment plan formulation for those conditions.

### Linkage in Treating Symptoms

From a symptom-management perspective, much of palliative medicine involves time spent treating pain, delirium, bereavement/depression/anxiety and nausea/vomiting. Each of these areas is the domain of psychiatry as well.

From a pain perspective, psychiatry has traditionally been one of the five avenues to subspecialty pain board certification (the other four being neurology, anesthesia, neurosurgery, and physical medicine and rehabilitation).





Psychiatrists are well-versed through their training to understand both opioid and nonopioid pharmacology — perhaps to a greater degree than any other primary specialty. Not only does psychiatry appreciate the pain relief component of the opioids, but the specialty is also adept at the detection and diagnosis of disease that is typically nonopioid responsive — nonmalignant pain as well as pain exacerbated by existential and behavioral factors. Adjunctive agents such as gabapentinoids and tricyclic antidepressants are utilized in psychiatry for a myriad of disorders, so there is a high degree of comfort with these agents too.

Additionally, psychiatrists have expertise in addictions and medication misuse. While traditionally there has not been a great deal of emphasis on medication misuse in the end-of-life population, as palliative medicine expands to assess and treat patients earlier in the course of their illness, this skill will become more important for the proper management of these patients.

With respect to the complications of bereavement, depression, anxiety and delirium, psychiatry is well-suited for the assessment and management of these disorders. Psychiatrists have a comprehensive understanding of the distinctions of these diagnoses and the differential diagnosis of patients with complex medical issues. From a medication management perspective as well as a psychotherapy standpoint, the psychiatrist finds fertile ground in this subject matter.

At first blush, few would expect psychiatry to be adept at nausea management. However, one must only remember the underlying pharmacology of antiemetics to realize that psychiatry comes to this topic with an in-depth understanding of the medications. Antiemetics work primarily at the site of the dopamine receptors in the brain, along the fourth ventricle, and most antiemetics are dopamine blockers, either directly or indirectly.

Psychiatrists have a long history of using dopamine blockade therapeutically to treat psychotic illness, and they have a deep appreciation of the uses of these medications, including their associated adverse effects. Some of these agents are being used off-label to treat refractory nausea/vomiting with great success (e.g., olanzapine). During a palliative medicine fellowship, physicians will improve their differential diagnosis and management of nausea and vomiting, and learn other appropriate interventions that may include gastric stenting or venting gastrostomy procedures; however, the majority of cases of nausea and vomiting are managed medically by agents familiar to psychiatric practitioners.

### Mutually Beneficial Specialties

In sum, there is significant overlap between the holistic orientations of psychiatry and palliative medicine, as well as diagnoses treated and symptoms addressed by both medical specialties. The basis of palliative medicine with family medicine and internal medicine can give psychiatrists a renewed and deepened understanding of the complete physical examination, as well as an enriched differential approach to the diagnosis of disease.

Likewise, psychiatry can lend to palliative medicine an in-depth and more thorough understanding of pain, improved behavioral differential diagnoses, and an increased understanding of addictions and medication misuse. ■

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# Understanding and Managing Psychosocial Risk Factors in Bariatric Surgery Patients

By Leslie J. Heinberg, PhD



Leslie J. Heinberg, PhD

Bariatric surgery is considered the most effective treatment for severe obesity (defined as body mass index  $\geq 40$  kg/m<sup>2</sup>), resulting in average weight loss of 35 percent of initial body weight as well as marked reductions in multiple medical comorbidities.<sup>1</sup>

However, unlike many other common surgeries, bariatric surgery is closely linked to behavior and psychosocial factors. Eating and exercise behaviors as well as psychological and social factors may have caused, exacerbated or maintained the severe obesity. Further, bariatric surgery candidates are a psychiatrically vulnerable population with a high level of psychiatric and psychosocial comorbidity.<sup>2-3</sup>

## Mental Health a Key Component of Bariatric Surgery Assessment

Although surgery results in significant anatomical alterations, long-term success requires significant behavioral change and necessitates that individuals adhere to permanent lifestyle alterations in diet and exercise as well as reduce reliance on food to cope with life stressors. Because of these factors, mental health professionals are an essential component of the multidisciplinary assessment and treatment team at most bariatric surgery treatment centers.<sup>4</sup>

The behavioral health team of psychologists is fully integrated into the multidisciplinary care and research at Cleveland Clinic's Bariatric and Metabolic Institute. We continue to focus our work on how to better identify, treat and manage psychosocial risk factors that may impede optimal success with surgery. The following reflects some of the research being conducted by our behavioral health team:

- Binge eating disorder (BED) was recently included in the DSM-5.<sup>5</sup> The lifetime prevalence rate for BED using the DSM-IV-TR<sup>6</sup> research criteria tended to be higher in bariatric surgery candidates than in the normative population; however, studies had not examined how many more bariatric surgery candidates will meet the new, less conservative criteria of DSM-5, which lowered both frequency and duration of binge eating that qualifies as a disorder. We obtained data from 1,326 bariatric surgery candidates. Of those patients, 297 (22.4 percent) were diagnosed with current BED using

## KEY POINTS

Bariatric surgery is closely linked to behavior and psychosocial factors, and bariatric surgery candidates are a psychiatrically vulnerable population.

The long-term success of bariatric surgery requires that patients make significant behavioral changes.

For these reasons, mental health professionals are an essential component of the multidisciplinary bariatric surgery assessment and treatment team.

DSM-IV-TR research criteria. Only a slightly greater percentage (an additional 3.43 percent) of bariatric surgery candidates met the diagnostic threshold for BED when using DSM-5 criteria. These individuals were demographically similar and produced similar psychological testing profiles when compared with patients who met DSM-IV-TR criteria.<sup>7</sup>

- Recent research has demonstrated clinically significant cognitive impairment is present in as many as 23 percent of bariatric surgery patients and that preoperative impairments predict weight loss outcomes at one year. We examined whether such impairments could contribute to poorer adherence. Cognitive testing and a self-report measure of adherence to postoperative bariatric guidelines were completed during a four- to six-week postoperative appointment for 37 patients who had undergone laparoscopic Roux-en-Y gastric bypass surgery. Rates of nonadherence were high, ranging from 24.3 to 78.4 percent depending on the recommendation. Strong correlations were observed between adherence to postoperative guidelines for physical activity, protein and vitamin intake, and cognitive measures of attention, executive function and memory.<sup>8</sup>
- Psychological evaluation of bariatric surgery candidates often includes standardized psychological testing. Preoperative scores on the Minnesota

Multiphasic Personality Inventory-2-Restructured Form were examined in the context of self-reported difficulties and behaviors at one month (N = 591) and three months (N = 329) postsurgery.<sup>9</sup> Scores on subscales measuring somatization and somatic concerns were related to greater somatic problems at both one and three months following surgery (e.g., excessive pain and nausea). Scores on internalizing emotional disorders (e.g., anxiety, demoralization) predicted psychological distress (e.g., grieving the loss of food) and three-month maladaptive eating (e.g., graze eating). Subscales measuring externalizing behaviors (e.g., impulsivity and disinhibition) also were related to maladaptive eating at three months. This suggests the importance of early identification of patients who may have complications shortly after weight loss surgery.

Bariatric behavioral health is a relatively new specialty but is likely to continue to grow as the obesity epidemic continues. Our collaborative, multidisciplinary team affords us the opportunity to investigate and treat psychosocial factors in order to optimize outcomes for our patients. ■

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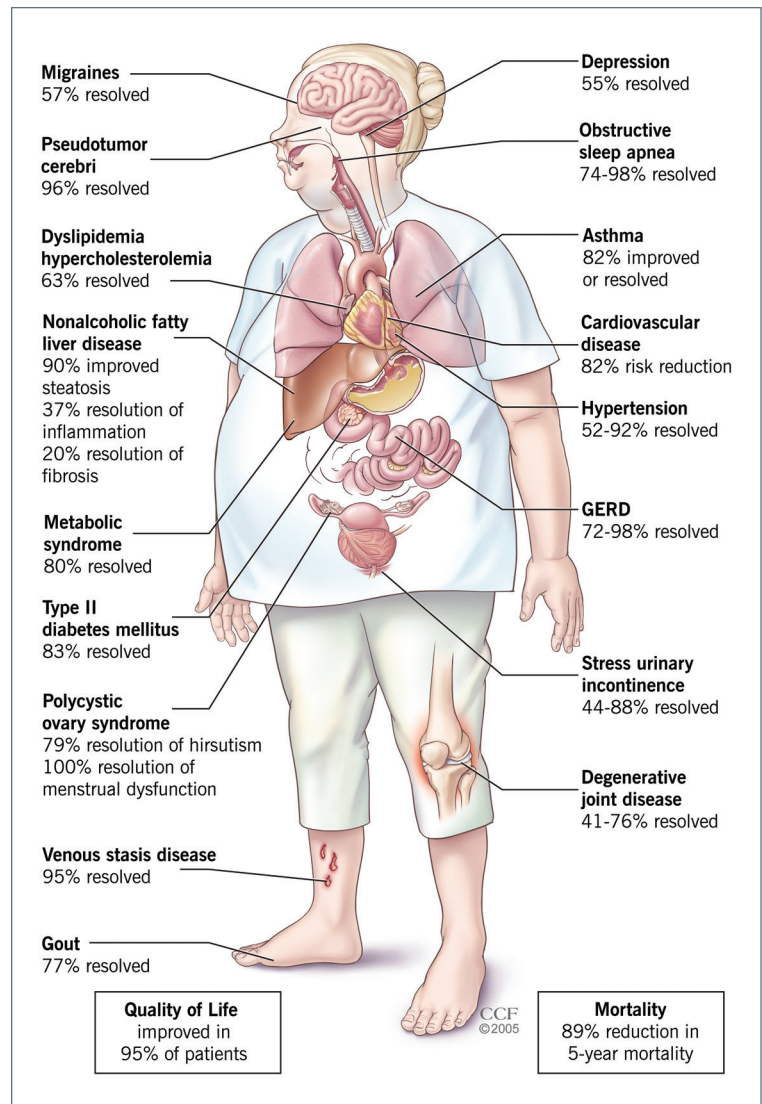


Figure 1. Positive outcomes from bariatric surgery.

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## Suicidal Thoughts in Patients with Epilepsy or Multiple Sclerosis

By Adele C. Viguera, MD, MPH



Adele C. Viguera, MD, MPH

**Patients with epilepsy and multiple sclerosis (MS) show high rates of depression and an increased risk for suicide. They also are more likely to think about death and self-harm than are individuals with other chronic illnesses, such as arthritis or cancer, according to a study of suicidal ideation conducted by Cleveland Clinic.**

Major depressive disorder (MDD) affects 20 to 50 percent of patients with epilepsy, MS, Parkinson disease or dementia. Depression adds to their disease burden, and suicide contributes substantially to excess mortality in this population.

### Increased Suicide Risk in Epilepsy and MS Patients

Suicide risk is eight times greater in epilepsy patients, compared with the general U.S. population. Identified risk factors include co-occurring psychiatric illness (especially MDD), female gender, older age, and early epilepsy onset or recent diagnosis. Similarly, suicide risk may be 1.8 to 7.5 times higher in MS patients. Risk factors include co-occurring psychiatric disorders, male gender, and early-onset MS.

Suicidal ideation is reported by individuals with many chronic medical conditions — such as 5 percent of arthritis patients and 8 percent of cancer patients, compared with 2.8 to 3.3 percent of the general population. Although epilepsy and MS patients have high suicide rates, surprisingly little is known about how often they think about self-harm.

### Retrospective Study Analyzes Suicidal Ideation Prevalence

Given these high rates, and to contribute to existing evidence, our group designed a nearly five-year retrospective analysis of the prevalence of suicidal ideation in patients seen at Cleveland Clinic's epilepsy and multiple sclerosis centers. As part of Cleveland Clinic's Knowledge Program — an initiative to compile discrete electronic clinical information for research, patient care improvement and quality measures — these centers systematically collect data from patient-entered, validated measures of health status and outcomes, including the Patient Health Questionnaire-9 (PHQ-9) screen for depression and the EQ-5D™ European quality-of-life scale.

### KEY POINTS

Patients with epilepsy and multiple sclerosis have high rates of depression and an increased risk for suicide, and they are more likely than other chronically ill patients to think about death and self-harm.

Our group conducted a retrospective analysis of the prevalence of suicidal ideation in patients seen at Cleveland Clinic's epilepsy and multiple sclerosis centers, using responses to the Patient Health Questionnaire-9 screen for depression.

Overall, 14.4 percent reported they had had thoughts of death or self-harm in the prior two weeks. The findings demonstrate that the PHQ-9 can be useful in identifying neurological patients who need additional clinical assessment for depression and suicide risk.

The PHQ-9 is intended to detect psychiatric symptoms of depression. It rates nine questions related to depression by frequency, from 0 to 3, with a 10th item to indicate overall severity. A total score of 10 to 14 indicates mild to moderate depression, 15 to 19 moderate to moderately severe depression, and  $\geq 20$  severe depression.

Item 9 of the questionnaire addresses the presence and persistence of recent thoughts of death or self-harm. Although there are high rates of false-positive results, this simple method has proved useful in screening for suicidal risk in primary care medical settings. Few patients identified by their PHQ item 9 responses later attempt suicide, but there is a significant association. A recent large retrospective study found that risks of attempted and completed suicide were 10 times greater among patients reporting elevated PHQ item 9 scores and increased with persistence of the elevated scores. In clinical samples with high rates of depression, PHQ item 9 can guide selection of patients who require closer assessment and who might benefit from psychiatric care.

Our study included all patients age 18 and older evaluated at the study sites between October 1, 2007, and August 13, 2012. The primary outcome measure was response to item 9 of the PHQ-9: “How often in the past 2 weeks have you thought you would be better off dead, or of hurting yourself in some way?” We considered PHQ item 9 scores  $\geq 1$  to be positive for putative suicidal ideation. A score of  $\geq 10$  on the other eight items (PHQ-8) was used to identify probable clinical depression.

We also extracted sociodemographic and clinical information from the Knowledge Program database, including age, gender, race, marital status, approximate household income and common medical diagnoses. Neurologic disease-specific measures included ratings with the Liverpool Seizure Severity Scale for epilepsy patients and the Multiple Sclerosis Performance Scales for MS patients.

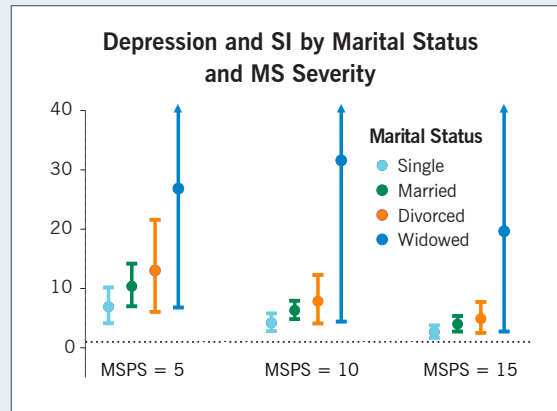
### Results Show High Depression, Suicide Ideation Rates

Our findings are based on 20,734 outpatient clinic visits by 2,763 patients diagnosed with epilepsy and 3,823 patients diagnosed with MS who completed the PHQ-9 at least once.

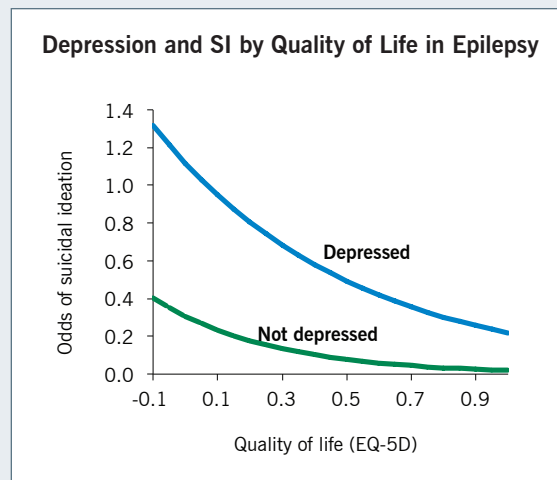
Statistical analysis showed a high rate of depression among epilepsy patients (37 percent) and MS patients (40 percent). Overall, 14.4 percent reported thoughts of death or self-harm in the prior two weeks. As expected, patients with depression were more likely to report suicidal ideation.

Among epilepsy patients, 14 percent reported thoughts of death or self-harm. Male gender was associated with putative suicidal ideation, but other demographic factors were not. Among MS patients, 14.7 percent reported thoughts of death or self-harm. Risk factors included male gender, Caucasian race, co-occurring medical disorders and lower health-related quality-of-life scores.

Suicidal ideation is difficult to quantify. Patient self-reports are based on subjective mental states that cannot be verified objectively. As stated previously, elevated PHQ item 9 scores have been associated with increased risk of suicidal behavior but almost certainly overestimate clinically significant suicide risk — or even the presence of suicidal ideation. Similarly, the clinical utility of suicidal ideation as a predictor of suicide risk is severely limited. The ratio of estimated rates of suicidal ideation to suicidal behaviors may be as high as several hundred to one.



**Figure 1.** Relative effect of depression on PHQ item 9 response increases as MS severity worsens and depends on marital status; higher MSPS scores indicate more severe disease. SI = Suicidal ideation; MSPS = Multiple Sclerosis Performance Scales



**Figure 2.** Relative effect of depression on PHQ item 9 response increases as QOL improves; in both groups, odds of positive item 9 decline as QOL improves; higher EQ-5D scores indicate better QOL. QOL = quality of life.

### Screening Tool and Intervention

Despite this study's limitations, we demonstrated that the PHQ-9 can be useful as a screening tool to identify neurological patients who need additional clinical assessment for depression and potential suicide risk. Cleveland Clinic's epilepsy and multiple sclerosis centers have specific protocols for patients who report thoughts of death or self-harm. A combination of the PHQ-9 total score, item 9 response and the clinician's assessment is used to determine whether a patient requires transfer to the emergency department for further psychiatric assessment. ■

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# Circulating Astrocytic Protein S100B May Indicate Blood-Brain Barrier Disruption Due to Childhood Emotional Trauma

By Tatiana Falcone, MD



Tatiana Falcone, MD

A glial cell protein called S100B is a validated, reliable biomarker of blood-brain barrier (BBB) disruption and brain injury.<sup>1</sup> In Europe, emergency departments are using a serum test for S100B to assess the severity of head injuries.

At Cleveland Clinic's Neurological Institute, we have found evidence that S100B could be useful as a biomarker for BBB breakdown triggered by childhood trauma and abuse. If further validated, a serum test for S100B might become a clinical tool to assess the severity of emotional injury and the need for intervention.

## Childhood Trauma Affects Adult Health

Severe trauma during childhood has been linked to long-term mental health and social problems. In the 1990s, the Centers for Disease Control and Prevention and the Kaiser Permanente managed healthcare consortium launched the Adverse Childhood Experiences (ACE) Study, seeking links between childhood trauma and adult health. More than 17,000 adult health maintenance organization patients completed a questionnaire about childhood abuse (emotional, physical and sexual) and exposure to substance abuse, mental illness, domestic violence and other adverse experiences. These early life events were found to be strongly associated with suicidality, alcoholism, depressive disorders, illicit drug use and chronic medical diseases in adulthood.<sup>2-5</sup>

Similarly, children exposed to trauma in the first eight years of life have been shown to have a higher risk of developing mood disorders, psychotic disorders and posttraumatic stress disorder (PTSD), compared with children who were not exposed to trauma.<sup>6,7</sup> Numerous studies have found associations between childhood maltreatment and other forms of trauma and subsequent alterations in brain development, particularly of the hippocampus and frontal cortex.<sup>8,9</sup>

Emotional trauma appears to be linked to neurobiological consequences, although the pathophysiologic mechanisms are not fully understood. Studies show that stress can activate an inflammatory response and impair BBB function. We and others<sup>10,11</sup> have hypothesized that severe emotional trauma sets off a peripheral inflammatory response, leading to cytokine production, glial cell activation and BBB breakdown. These changes could potentially alter brain structure, cognition and behavior.

## KEY POINTS

Investigators at Cleveland Clinic, Case Western Reserve University and Ludwig Maximilian University in Munich, Germany, are studying the protein S100B as a biomarker for blood-brain barrier disruption related to childhood emotional trauma.

Blood levels of S100B are increased in adolescents exposed to emotional trauma as children, whether exposure was chronic, severe or early (before age 8).

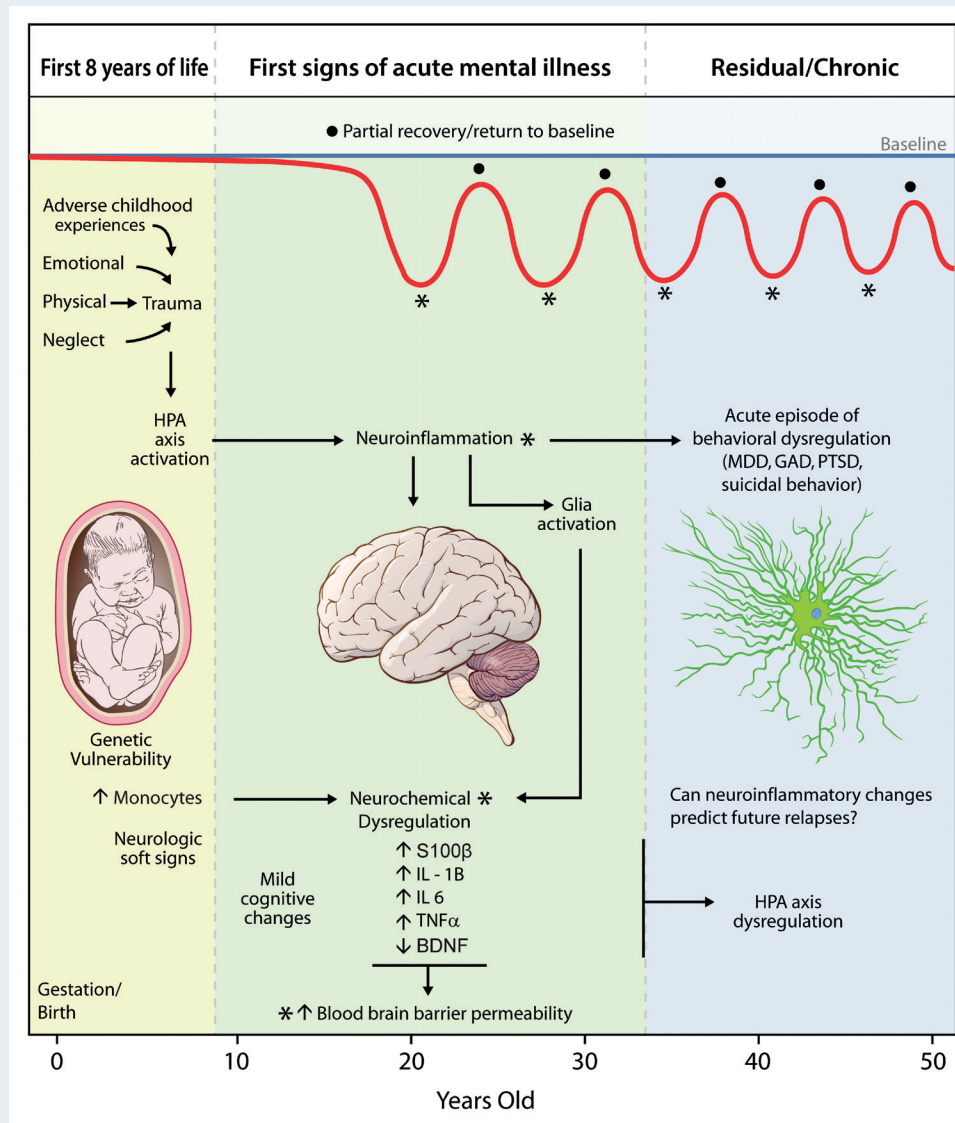
Mean S100B levels show a graded effect; adolescents exposed to two or three trauma types have higher S100B levels than those with less trauma exposure.

As a potential biomarker of CNS injury, S100B has been described as "the CRP (C-reactive protein) of the brain."<sup>12</sup> S100B is an astrocytic protein that can leak into the blood circulation when the BBB is breached. Elevated serum levels of S100B are not specific but have been associated with schizophrenia, bipolar disorder, depression, Alzheimer disease and epilepsy, as well as traumatic brain injury.

Our group first examined S100B as a potential biomarker of BBB function in suicidal adolescents with major depressive disorder and acute psychosis.<sup>13</sup> A subscale of the Brief Psychiatric Rating Scale for Children (BPRS-C) quantified suicidality. Mean S100B values were 0.152  $\pm$  0.020 ng/mL in children with low suicidality (BPRS-C subscores 1 to 4), compared with 0.354  $\pm$  0.044 ng/mL in those with high suicidality (BPRS-C subscores 5 to 7). Compared with healthy controls, suicidal adolescents had significantly higher serum S100B levels ( $p < .05$ ), independent of psychiatric diagnosis.

## Can Emotional Trauma Alter BBB?

Recently, we used serum S100B as a biomarker to investigate whether childhood emotional trauma can alter the BBB.<sup>14</sup> This study population included 88 psychiatric



**Figure 1. Emotional trauma as a trigger for mental illness.**

During the first eight years of life, the impact of emotional trauma can trigger hypothalamic-pituitary-adrenal (HPA) axis dysregulation and increased inflammatory response (elevated monocytes). Monocytes can cross the blood-brain barrier (BBB). A more recent hypothesis suggests brain injury is caused by BBB disruption, leading to an influx of monocytes in the central nervous system. Activated monocytes can trigger neuroinflammation in glial cells and perpetuate cytokine and S100B production. Each traumatic episode triggers the inflammatory response and alters the BBB. When traumatic episodes occur early in life, they can alter brain development. Patients begin experiencing cognitive dysfunction, emotional lability and memory problems, probably related to increased BBB permeability.



inpatients age 12 to 18 (64 with psychosis and 24 with mood disorder) and 20 healthy adolescent controls. A detailed psychiatric history and the Life Events Checklist (LEC) documented risk factors for childhood trauma, characterized as three types:

- Early onset (age < 8 years)
- Chronic (persisting for > 6 months)
- Severe (LEC score > 20)

The LEC assesses exposure to sexual abuse or other unwanted sexual experience, natural disasters, emotional neglect, death in family, fire or explosion, serious accident, toxic substance, physical assault, assault with a weapon, combat, captivity, life-threatening illness, severe human suffering, violent death and serious injury.

We also collected blood samples for S100B analysis. The inpatients with childhood trauma showed increased S100B blood levels, independent of psychiatric diagnosis, compared with controls and inpatients with no trauma history. Among the 30 inpatients without childhood trauma, the mean LEC score was 3.6 and mean S100B was .150 ng/mL. The 58 adolescents who experienced childhood trauma had a mean LEC score of 11.71 ( $p < .0001$ ) and mean S100B of .320 ng/mL ( $p = .001$ ).

All trauma types — early, chronic and severe — were associated with increased S100B levels. Mean S100B levels showed a graded effect (one type, ~0.2 ng/mL; two types > 0.3 ng/mL; three types ~0.5 ng/mL). The healthy controls and inpatients without trauma exposure had a mean S100B < 0.2 ng/mL. We concluded that a history of childhood emotional trauma may be associated with BBB impairment in adolescent psychiatric patients.

### Inflammatory Response May Be Damage Mechanism

This study, along with others, suggests that emotional trauma can cause long-term changes to the brain, possibly by way of an inflammatory response. The next step may be to use neuroimaging to compare levels of inflammatory markers with structural changes in the hippocampus or frontal lobe.

Of course, the most exciting potentiality would be to change the trajectory of a brain trauma so that intervention with medication or psychotherapy could prevent depression, psychosis or PTSD from developing. ■

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