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Suicidal Ideation in the Epilepsy Monitoring Unit: Predictive Risk Markers and their Application to Clinical Tool Development

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**Suicidal Ideation in the Epilepsy Monitoring Unit: Predictive Risk Markers and  
their Application to Clinical Tool Development**

By

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A thesis submitted in partial satisfaction of the

Requirements for the degree of

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A special thank you to Dodd Gray for his ongoing encouragement. This thesis is dedicated to my biggest supporters and lifelong teachers, my parents.

# **PART 1: LITERATURE REIVIEW**

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II: DEPRESSION AND SUICIDE

III: SUICIDALITY IN PEOPLE WITH EPILEPSY

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V: IRRITABILITY IN EPILEPSY

VI: TREATMENT FOR SUICIDALITY

VII: STATISTICAL APPROACHES FOR SUICIDE  
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## **SECTION I:**

### **EPILEPSY**

#### Epilepsy, Seizures, and Diagnosis

##### ***Epilepsy Defined***

Epilepsy is a common, and often chronic, neurological disorder characterized by recurrent seizures. Epileptic seizures are unprovoked episodes of abnormal synchronous electrical discharges in the brain, which cause behavioral changes such as uncontrolled movements, automatisms, staring, or loss of consciousness (Chang & Lowenstein, 2003).

##### ***Epilepsy by Numbers***

Epilepsy is the fourth most common neurological disorder in the United States, after Migraine, Stroke, and Alzheimer's Disease (Hirtz et al, 2007). Point prevalence of the condition is 0.5% to 1%, but risk increases with age. *Epilepsy across the spectrum*, a report compiled by the Institute of Medicine in 2012, estimated that 1 in 13 people will have a seizure at some point in their lives, and 1 in 26 people will be diagnosed with epilepsy (England et al, 2012). Epilepsy incidence resembles a U shaped curve, with highest risk in children and elders after a lower risk interval in the middle of the life course (England et al, 2012).

##### ***Features of Epileptic Seizures***

Epileptic seizures are said to be “unprovoked” to distinguish them from seizures secondary to temporary predisposing conditions such as severe metabolic imbalances, drug or alcohol withdrawal, mass effects caused by neoplasms or infection, and injury related to strokes or trauma. These provoked seizures usually resolve once the primary condition is treated, and are not considered to be “epilepsy”. Abnormal neurophysiological signs are also crucial to the definition of epilepsy. Electrical discharges associated with epilepsy, but not other causes of spells, can be captured by electroencephalogram(EEG).

##### ***Epilepsy Monitoring Units(EMU) and Seizure Evaluation***

Despite the arsenal of anti-epileptic medications available, close to one third of patients will not reach optimal seizure control (Sanders et al, 1993). These patients with refractory seizures may require a multiday inpatient stay in an EMU to be monitored by video and EEG in a safe

environment as a seizure occurs (Kumar-Pelavo et al, 2013). EMU monitoring may allow further description of seizure location, spread, and etiology subtyping can be done based on EEG, imaging, and other studies. In addition, new diagnostic information allows for evaluation and safe implementation of new treatment strategies such surgical resection of epileptogenic foci, and transitioning to a different anti-epileptic drug (Hui et al, 2007).

## **The Economic and Psychosocial Costs of Epilepsy**

### ***The Economic Burden of Epilepsy***

Whether considering the economic cost on a national scale, or the psychosocial and medical cost at the individual or family level, the impact of epilepsy is significant. The annual direct medical costs for epilepsy care in the United States is 9.6 billion dollars (England et al, 2012). When accounting for direct and indirect costs, the reported burden of epilepsy in the United States is 12.5-15.5 billion dollars each year (England et al, 2012, Begley et al, 2000).

### ***The Psychosocial Implications of Epilepsy***

As with many other chronic diseases, living with epilepsy is associated with psychosocial challenges such as living with stigma, decreased overall quality of life, and increased prevalence of psychiatric disease.

One important contributor to decreased quality of life in epilepsy is stigma. Stigma leads to internalized negativity, social isolation, and discrimination. This both harms internal emotional wellbeing and limits external opportunities, which culminates in poor psychiatric and psychosocial outcomes (Major et al, 2004). As an example of how this nebulous concept may translate to deleterious changes in behavior, a 2008 study found that more than a third of teenaged students with epilepsy keep their diagnoses private from teachers to avoid stigma (Baker et al, 2008). Though such concealment may seem maladaptive and likely leads to resource underutilization, such apprehension must be viewed in cultural and historical context. As the neurologist Rajendra Kale describes, *“The history of epilepsy can be summarized as 4000 years of ignorance, superstition and stigma, followed by 100 years of knowledge, superstition and stigma”* (Kale, 1997).

Epilepsy has been described since the writings of Hippocrates, who called it the “sacred disease”, and its previous cures have included exorcism (Temkin, 1971). While these associations are much less powerful today, they are not comfortably distant in the past. There is for instance the story of Annaliese Michel which occurred in 1976 in a small town in Germany, and was recently popularized by the 2005 movie *The exorcism of Emily Rose* (Goodman, 2005). Annaliese Michel was a woman with epilepsy who died of starvation and exhaustion at 23 years of age due to therapeutic exorcism (Goodman, 2005). This type of history is not as far in the past of the United States either; people with epilepsy (PWE) were not allowed to be married in 17 states until 1956, and excluding PWE from businesses was legal until the 1970s (Kale et al, 1997).

Overall, academic, employment, and social opportunities appear to be more limited in PWE. Data from the 2002 National health survey showed that a non-clinical sample of 30,000 people with seizures were significantly more likely to have not completed high school or college, be divorced or never married, and to have formally worked but be currently unemployed or never have been employed (Strine et al, 2005). This study goes on to list significantly higher levels of worthlessness, restlessness, hopelessness, anxiety, depression, chronic pain, and insomnia (Strine et al, 2005). Additionally, losing a driver’s license due to seizures further isolates PWE professionally, practically, and socially.

However, of all contributors to quality of life, the most significant has reliably been mental health, specifically mood disorders such as depression and anxiety.

## **SECTION II: DEPRESSION AND SUICIDE**

### **A Brief Overview of Major Depressive Disorder**

#### *Epidemiology of Depression*

is one of the most common psychiatric conditions, and is the leading cause of disability in developed countries (Kessler et al, 2005). MDD has a prevalence of 6.7% in the U.S. general population and a 16.5% lifetime prevalence (Kessler et al 2005a and 2005b). However, among patients with chronic medical conditions, the average prevalence is 25%, and varies by condition (Meader et al, 2011). Depression is especially high in conditions affecting the central nervous system, such as traumatic brain injury, stroke, parkinsons disease, and epilepsy. Inflammatory conditions and cancer comorbidities also have disproportionate comorbidity (Jorge et l, 2004; McDonald et al, 2003; Whooley et al, 2006; Reiche et al, 2004; Hanly et al, 2005).

#### *Depression Defined*

According to the Diagnostic and Statistical Manual for Mental Disorders V, a Major depressive disorder(MDD) episode is characterized by a period of 2 weeks or greater that is characterized by two core symptoms, anhedonia and low mood, and seven additional symptoms: sleep dysregulation, low energy, psychomotor changes, guilt and low self-esteem, concentration difficulties, appetite dysregulation, and self harm or suicidal ideation or intent (American Psychiatric Association, 2013). Presence of five out of nine of these symptoms with at least one being depressed mood or anhedonia and significant functional impairment are required for diagnosis (American Psychiatric Association, 2013). Though diagnostic definitions focus on a two-week interval, MDD is often a chronic condition: After one episode, an individual is estimated to have a 50% chance of subsequent episodes with increasing risk with each subsequent episode, making treatment important for prevention purposes (American Psychiatric Association, 2000).



### ***The importance of screening***

In the absence of universal screening, it has been estimated that only half of depression cases will be identified in a primary care setting (Mitchell et al, 2009). If not asked about mood, patients tend to not bring it up. Alternatively, about 2/3 of patients present with somatic symptoms such as headache, fatigue, or chronic pain (Bell et al, 2011, and Simon et al, 1999).

### ***The cost of unidentified and untreated depression***

Unidentified and untreated depression leads to loss at all levels: patients have a decreased quality of life (Trivedi et al, 2010), worse comorbidity outcomes (Moussavi et al, 2007), increased risk of suicide, and increased general mortality (1.81) ( Cuijpers et al, 2002)., spouses (Fadden et al, 1987) and children (Olfson, 2003) are affected. There are also economic losses, with both patients and direct employers being affected; depression accounts for the largest losses due to disability of all medical conditions (Wang et al, 2003)

### ***Tools for Assessing Depression outside of Psychiatric Settings***

Three main tools are used to screen for depression in non-psychiatric clinical practice: the Beck Depression Inventory, the PHQ-2 and the PHQ-9 (Williams, 2015). Of these, the PHQ surveys may be preferable due to open-access use and reproduction policies. The PHQ-9 corresponds almost perfectly to the 9 symptoms for depression outlined in the DSM, but uses plain language to allow for patient self report (Spitzer et al, 2001; DSM IV). A newer version, the PHQ-8 was also recently introduced. This version includes all but the suicidal ideation question (Kroenke, 2009). Some believe it was developed to evade liability issues or discomfort associated with asking patients about suicidal ideation (Simon et al, 2013).

Avoiding questions regarding suicidality when screening for depression may have consequences, as more than 90% of suicides occur in the context of psychiatric disease, usually depression. Suicide is a feared consequence of depression, and is considered by some to represent a “fully preventable death” (CDC national health report, 2010).

## **Suicide: A General Perspective**

### ***Suicide by Numbers in the US and Worldwide***

Globally, approximately 1 million people a year die by suicide, with close to 40,000 deaths occurring annually in the United States (Murray et al, US burden of disease collaborators, 2013). This translates to one suicide death every 40 seconds. Importantly, these values are widely considered to be underestimated due to factors such as social stigma and death certification practices (Hawton et al, 2009). Even so, suicide remains the tenth leading cause of death worldwide, the 3<sup>rd</sup> leading cause of death in adolescents and the 2<sup>nd</sup> leading cause of death in college students (Hawton et al, 2009).

## **Risk Factors for Suicide in the General Population**

### ***Suicide Ideation and Attempts***

Every year, 650,000 people in the US receive emergency treatment after attempting suicide, while 40,000 people die by suicide, leading to completion rates of approximately 1 in 17 (Goldsmith et al, 2002). Many see suicidal behavior as occurring on a continuum, with suicidal ideation, non fatal self-harm, and suicide attempts serving as precursors to completion. Indeed, prior attempts are currently believed to be the best predictive factor for future attempts and suicide completion (Kessler et al, 2005). Though history of attempt is a key risk factor, it is not always present. Only 19% of suicide victims have a history of attempts (CDC homicide and suicide report, 2006). Similarly, a history of attempt need not lead to death by suicide, as there are 10-40 failed suicide attempts for every completion (US burden of disease collaborators, 2013). Clinically, attempts represent an important opportunity for mental health intervention. Academically, attempts represent a window into the mental state which culminated suicidal behavior.

### ***Psychiatric Disorders***

It is often stated that suicide is a complication of psychiatric disorders (Cavanagh et al, 2003). Indeed, 95% of suicide victims have a diagnosable psychiatric disorder, with depression, borderline personality disorder, substance abuse and bipolar diagnoses being especially associated with suicide (Tidemalm et al, 2008). Anxiety disorders also play a role, especially when combined with depression; patients with both had a suicide odds ratio of 17 (Sareen 2005, Bolton et al, 2008). Of the substance disorders, alcohol abuse is an especially well documented risk factor, and is thought to contribute more than other substances partly because it increases impulsivity (Meyer et al, 2014). 16.5% of suicide victims have known alcohol-related problems (CDC homicide and suicide report, 2006). Reported rates of suicidal behavior in individuals with alcohol use disorder ranges from 2-18 percent, depending on the study (Roy et al, 1986, Murphy et al, 1992). Alcohol intoxication is also often involved in the act of suicide. In a CDC study of suicide victims from 13 states, one third tested positive for blood alcohol (CDC, 2006).

### ***Sex, Age and Race, sexual orientation***

Male sex is also a well-established risk factor for suicide completion. Although women attempt suicide 4 times more often than men, men are 3 times more likely to complete suicide (Spicer et al, 2000). This discrepancy is thought to be largely due to choice of method, as rates of completion stratified by method do not differ by sex (Miller et al, 2004). Suicide increases with age, though young adults are most likely to attempt suicide (Miller et al). In terms of race and age, the two highest risk groups are elderly white males and young black males (Miller et al, 2004, Joe et al, 2006). There are also increased rates of suicidal ideation among adult gay men and lesbians, with approximately 12% of individuals reporting a history of at least one suicide attempt (Bagley & Tremblay, 1997; Herrell et al, 1999; Paul et al, 2002).

### ***Occupation and Economic Factors***

Occupational and economic factors may also play a role in suicide risk assessment. A meta-analysis of 34 studies found that lower-skilled and unskilled workers are at higher risk for suicide than skilled workers with

1.8 and 0.7 rate ratios, respectively (Milner et al, 2013). Unemployment and financial strain also increases risk for suicide (Chang et al, 2013).

### ***Isolation, Marital Status, and Familial Factors***

Isolation, though challenging to quantify, is a crucial risk factor for suicide. For instance, living alone, regardless of marital status, increases risk of suicide (Heikinnen et al, 1995). Marital status and children are also important: risk is highest in those that have never been married, followed by those who have been widowed, separated, divorced, married without children and married with children (Spicer & Miller, 2000).

Exposure to familial suicide and heritability are also contributory. Family history of suicide in a first-degree relative increases risk by 6-fold (Goldsmith et al, 2002). Heritability is between 30% - 50% but it remains unclear whether it is the suicidality or psychiatric disease that is heritable (Goldsmith et al, 2002, Qin et al, 2002). Environmental factors are also important, as having a non-related spouse commit suicide greatly increases risk (Agerbo et al, 2003).

In summary, many risk factors have been identified and are currently used for clinical risk assessment, including history of suicidal behavior, psychiatric disease, demographics, occupational factors, social factors, and family history.

## **SECTION III: SUICIDALITY IN PEOPLE WITH EPILEPSY**

### ***Psychiatric Comorbidity in Epilepsy***

People with epilepsy (PWE) face disproportionately high rates of psychiatric comorbidity. Depression is most common, with respective rates of 17% - 55%, depending on the setting and study (Jones et al, 2005 ; Mendez et al, 1986). Anxiety disorders are also prevalent, with rates of 11% - 30% (Jones et al, 2005 ; Gaitatzis et al, 2004 ; Jacoby et al, 1996). Though they are pervasive, mood disorders are also under-recognized and under-treated in PWE (Hermann et al., 2000). Importantly, failure to address mood disturbances occurs despite established safety of using antidepressants such as sertraline and the known detrimental impact on both seizure-related outcomes and quality of life in general (Kanner et al, 2000; Boylan et al, 2002; Johnson et al, 2000).

### ***Suicide Risk in Epilepsy***

Psychiatric concerns in PWE extend beyond mood disorders into the realm of self-harm and suicidality. Many studies have probed the epidemiology of this phenomenon with varying outcomes, but a five-fold increase in suicide rate is most commonly cited with the caveat that this risk is further enriched to 6-25 fold if the seizures are focal, especially if the focus originates from the temporal lobe (Harris & Barraclough, 1997). Individual studies have reported suicide rates ranging from 0-25% in PWE, and a meta-analysis recently found close to a ten fold higher risk in PWE than the general population (Pompili et al, 2005).

### ***Suicidal & Parasuicidal Behavior in Epilepsy***

Similar patterns can be appreciated when considering suicide attempts, self-harm, and suicidal/self-harm ideation (SSHI). In the general population, a conservative estimate of the suicidal ideation, attempts, and completion ratio is 100:10:1 (Swedish National Council for Suicide Prevention, 1997). In the general population, attempts: completions are highest in adolescents (~200:1), and lowest in the elderly (~4:1). Suicide attempts, like suicide, are more common in PWE, and may show a different ratio for ideation: attempts: completion than in the general population. In PWE, the ideation:self-harm ratio was found to be nearly 1:1 in a representative sample, indicating that it may be prudent to place more weight on presence of suicidal thoughts in PWE (Rai et al, 2012).

Self-harm prevalence in PWE was actually noted by general suicide researchers many decades ago, when descriptive analyses of emergency department admissions for self harm were found to be heavily enriched for PWE. Self-poisoning admissions were especially enrichment for epilepsy as compared to the general population, and it is now well-established that PWE tend to use their prescribed anti-convulsant medications for self-poisoning (MacKay 1979, Hawton et al, 1980). Importantly, PWE tend to repeat self-harm/suicide attempts more frequently than other self-injuring patients with repetition rates of 74% as compared to 39% (MacKay, 1979).

Self-harm in all forms, not just as self-poisoning, is more common in epilepsy than in other chronic physical diseases or in control inpatients without chronic health concerns (Singhal et al, 2014). When self-harm relative risk (RR) in 23 chronic physical and psychiatric illnesses were compared, Epilepsy had the highest associated relative risk for self-harm of all physical illnesses, with an RR of 4 in the year after diagnosis which leveled off to 3 thereafter. Furthermore, Epilepsy was the only disorder to straddled the large RR gap between physical illnesses (with showed RRs between 1-2) and psychiatric conditions (which showed RRs of 5 or greater) (Singhal et al, 2014). With comorbid psychiatric disease and epilepsy, the self-harm RR jumps to 14, indicating self-destructive synergy.

Suicidal/self-harm ideation (SSHI) follows the same general trend seen with psychiatric disease, suicide and suicidal behavior in PWE. Depending on the study, 25-40% of patients with epilepsy have experienced SSHI (Tellez-Zenteno et al, 2007, Boylan et al, 2004, Rai et al, 2012).

## **SECTION IV: SUICIDALITY SCREENING IN EPILEPSY**

### *Screening, Prediction, and Prevention Approaches for Suicidality in Epilepsy*

Though most people with suicidal ideation will not commit or attempt suicide, recognizing ideation is an important intervention point, as it is a necessary predecessor to suicidal acts (McAuliffe, 2002). The temporal onset of suicidal ideation is also important, as 60% of those who do make an attempt will do so within the first year of ideation onset (Nock et al, 2008).

Furthermore, the general clinical duty of self-harm and suicide prevention may be more pertinent in PWE for several reasons. Ready access to medications useable in overdose is a known problem. Two-thirds of PWE admitted for self harm used anti-epileptic drugs (AEDs) to poison themselves (Meyer et al, 2014). Integration of psychiatric status with neurological care would also improve clinical decision making. For instance, choosing an anti-depressant that does not lower seizure threshold and an anti-epileptic that is not readily usable for self-poisoning are practical improvements in care that hinge on clinician awareness of psychiatric state. Lastly, self-harm is damaging in its own right, and suicidal ideation may be indicative of more severe psychiatric suffering that may be alleviated with pharmacological or therapy-based suicidality interventions.

### *Opportunities for Integrating Mental Health into Epilepsy Care*

Suicidal patients are known to routinely see health providers in the weeks or months before their death (Luoma et al, 2003). Protecting suicidal patients from themselves is a fundamental duty of a physician, as is avoiding foreseeable mortality (Jobes 2003). Though foreseeability is challenging with suicide and screening requires resources, attempting to address suicidality and prevent it is an imperative with patients at high risk for psychiatric disease and suicide.

In many ways, epilepsy monitoring units (EMUs) are an ideal setting for probing mental health concerns. In general, psychiatric disease and suicidality burden is highest in these inpatients than epilepsy center outpatients, and least common in community based samples who do not need regular epilepsy care. EMUs also have an inpatient setting that is not medically acute for some portion of the observational stay. One of the most discussed challenges is the division between neurological and psychiatric specialties, which tend to be functionally isolated in

practice, despite high psychiatric comorbidity in epilepsy, Parkinson's disease, multiple sclerosis, and post-stroke depression (Kanner et al, 2003).

Overcoming such challenges can create large returns on investment in this setting. In one interventional study done at Dartmouth Epilepsy Center, collocating a psychiatrist in epilepsy unit for one afternoon a week (0.1 Full Time) led to a decreased level of anxiety and/or depression in 84% of patients as measured by the GAD-7 ( $4 \pm 0.4$  point improvement) and PHQ-9 ( $4.6 \pm 0.4$  point improvement) (Chen et al, 2014). Furthermore, there are large economic motivators. Mental health issues are a strong predictor for 30-day readmission into the EMU and Emergency Departments (Caller et al, 2014).

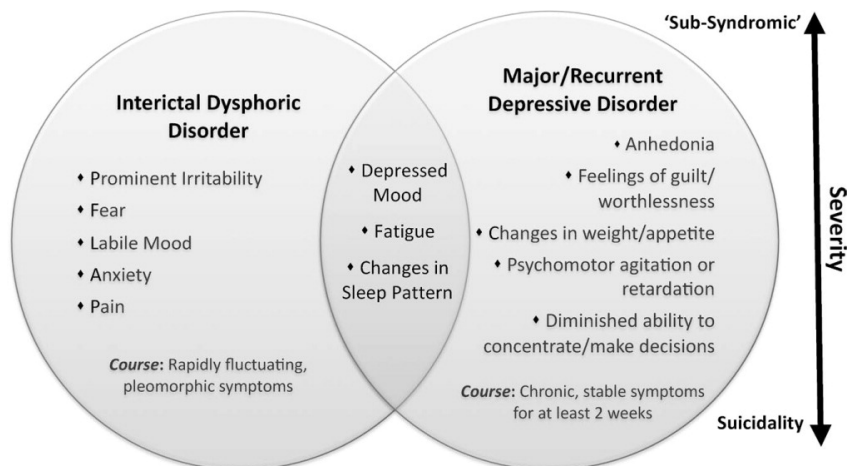


## SECTION V: IRRITABILITY IN EPILEPSY

### *Non-Classical Features of Depression in PWE*

In some ways, depression in PWE does not present classically. In a study performed by Kanner and colleagues that evaluated 97 consecutive patients with epilepsy who were referred to psychiatry, 69% of the patients with depression presented with “pleomorphic” picture, with 36% of the patients noting irritability as their predominant depressive symptom (Kanner et al, 2000). This team suggested a different diagnosis for this atypical depression, “dysthymic-like disorder of epilepsy”, because many PWE do not meet criteria for depression due to the atypical symptomology and presence of symptom free periods. They described this symptom profile as “anhedonia, with or without hopelessness, fatigue, anxiety, irritability and poor frustration tolerance, and mood lability with bouts of crying” (Kanner et al, 2000, Kanner and Barry 2001).

This team was not the only group to advocate for the creation of a new disorder to clearly capture stereotypical differences in mood disorders presentations for PWE. Blumer and colleagues coined the term “interictal dysphoric disorder” (IDD). In IDD, paroxysmal events that range from “irritability to impulsive aggression to frank rage in association with depressive features” vary temporally with seizures, causing an interictal mood disorder (Blumer et al, 2000).



**Figure 1: Shared and disparate features of Interictal Dysphoric Disorder and Depressive disorder**

*reproduced from Rayner et al, 2012*

While recurrent bouts of depression and IDD have depressed mood, fatigue and sleep in common, they differ by the addition of lability, irritability, anxiety, fear and pain. Notably, anhedonia, one of two core features of depression, is not part of this construct (Rayner et al, 2012).

Yet another suggestion is the use of the term “epileptic personality” to capture the rampant prevalence of irritability in epilepsy along with its connection to psychiatric disease ( Yazici et al, 2014). More expert consensus will need to develop before either viewpoint prevails; however, the benefits of improving patient care with these descriptions should always be considered alongside the potential cost of adding stigma to an already misunderstood burden by equating personality with mental illness. As an illustration to past missteps, a dated, near century-old article on the “epileptic personality”, defines it as “egocentricity, supersensitiveness, irritability, emotional poverty and stiffness of mentation” (Notkin et al, 1928).

There is still a lack of consensus in the field at large about whether psychopathologies in PWE are truly distinct, and if so, if creating new terms would improve clinical care or distance care-takers outside of specialized epilepsy mental healthcare (Kanner & Barry, 2001). Furthermore, many still believe that features like irritability are not the norm, but are instead markers of other comorbidities besides epilepsy and depression: for instance, one review of 44 PWE who do exhibit aggression showed that interictal aggression is usually associated with developmental disabilities, psychosis, and CNS pathologies such as trauma or encephalitis which then cause secondary seizures, rather than primary epilepsy (Mendez et al, 1993). Others point to comorbid anxiety disorders as the cause of features like irritability.

### ***Irritability & Similar Features in Other Disorders***

Though these previous paths of research may suggest that irritability is an epilepsy-specific risk factor, there are also insights that may suggest otherwise. For instance, irritability is a common thread that connects many other high suicide risk conditions, including Bipolar Disorder Borderline personality disorder, Alcohol dependency, Attention Deficit

Hyperactive Disorder and Adolescents (Benazzi & Akiskal, 2005; Stone et al, 1988; Wojnar et al, 2009; Hinshaw, 2012; Dougherty et al, 2009).

When the term “irritability” is not specifically used, similar conceptualizations such as “reactive aggression” or “impulsivity” are applied, and these terms are likely to be highly inter-related. Notably, a decision tree analysis of suicidality prediction found aggression to be an early decisive node for separation of recent and distant suicide attempters with borderline personality disorder, suggesting these very distinguishing features may also relate to suicide (Mann et al, 2008). Further work must be done to fully understand the operational meaning of these terms and compare these high risk groups in a single study assessing irritability, impulsivity, and reactive aggression to tease these elements apart and distinguish how population-specific or broad these relationships truly are.

## **SECTION VI: TREATMENT FOR SUICIDALITY**

Detection of suicidality is clinically relevant because there are therapeutic approaches for addressing self-harm risks. Furthermore, risk is often acute and temporary, motivating responsive treatment during periods of acute risks.

### ***Pharmacological Treatment of Suicidality***

Pharmacological treatments have not been historically promising (Simon et al, 2013). The main approach has been to treat suicidality by treating depression with anti-depressants, most notably serotonin specific reuptake inhibitors (SSRIs). While ecological studies at the country scale show decreased suicide rates with increased SSRI prescription rates, the utility of SSRIs for suicide prevention has been controversial (Mann et al, 2005, Fergesson et al, 2005). To put it quantitatively, a recent meta-analysis of all published randomized control trials showed increased suicidality in patients given SSRIs over placebo with an odds ratio(OR) of 2.28 (Fergesson et al, 2005). Though depression is one of the most potent risk factors for suicide, applying depression treatment does not account for the importance of other features linked to suicide, such as agitation, irritability, and insomnia, which may become exacerbated with SSRI administration. Other pharmacological treatments that have been more experimentally implemented include Lithium, and depot flupenthixol given acutely, but these also have limited efficacy (Furgesson et al, 2005).

Fortunately, the pharmacological picture is somewhat more optimistic in epilepsy, as ample opportunities to manipulate psychotropic effects via anti-epileptic choice exist. For instance, some GABA-mediated AEDs may be more more likely to induce suicidality, irritability, and mood changes, including topiramate, levetiracetam, vigabatrim, and tiagabine (Mula et al, 2003). Meanwhile, sodium-channel mediated anti-convulsants can have positive psychotropic effects, most notably lamotrigine, carbamazepine, and valproic acid (Ettinger et al, 2006, Andersohn et al, 2010). The epilepsy monitoring unit is an ideal safe setting for altering pharmacological seizure management, giving further motivation for detection of psychiatric issues integration of mental health into epilepsy

care at this time point.

### ***Behavioral Treatment for Suicidality***

In the general population, most effective treatments for suicidality have been therapy based, especially when therapy is targeted for the specific population (Fergusson et al, 2005). As with most psychiatric conditions, cognitive behavioral therapy is likely to help address irritability, and potentially related impulsivity or reactive aggression. However, drawing additional tactics from other high suicidality and high irritability populations with tailored therapy modalities is also another option. For instance, mindfulness-based therapy is specifically found to be helpful for impulsivity and irritability, which moderate suicide risk in ADHD (Alderson et al, 2013). Dialectical therapy is traditionally used for suicidality in Borderline Personality disorder (Linehan et al, 2006). Problem solving therapy has been applied in elders with suicidality. Though no epilepsy specific approaches exist, these represent a variety of techniques to pick through for an epilepsy-tailored approach.

## **SECTION VII: PREDICTIVE RISK ASSESSMENT**

### *Statistical and Clinical Risk Assessment*

Suicide risk prediction has been among the most coveted goals in suicide research for many decades, and remains an elusive problem today. Though suicidality assessment is a challenging statistical and clinical problem, statistical and actuarial methods have long been established as superior to clinical judgement, with a recent meta-analysis spanning 56 years of studies providing further confirmation (Meehl et al, 1954, Ægisdóttir et al 2006). The cost-benefit analysis of adding statistical methods to suicide risk assessment is especially favorable with high risk populations such as patients with seizures, who represent high baseline suicidality and therefore should have a lower screening threshold and lower false positive rates (Podolak, 2015).

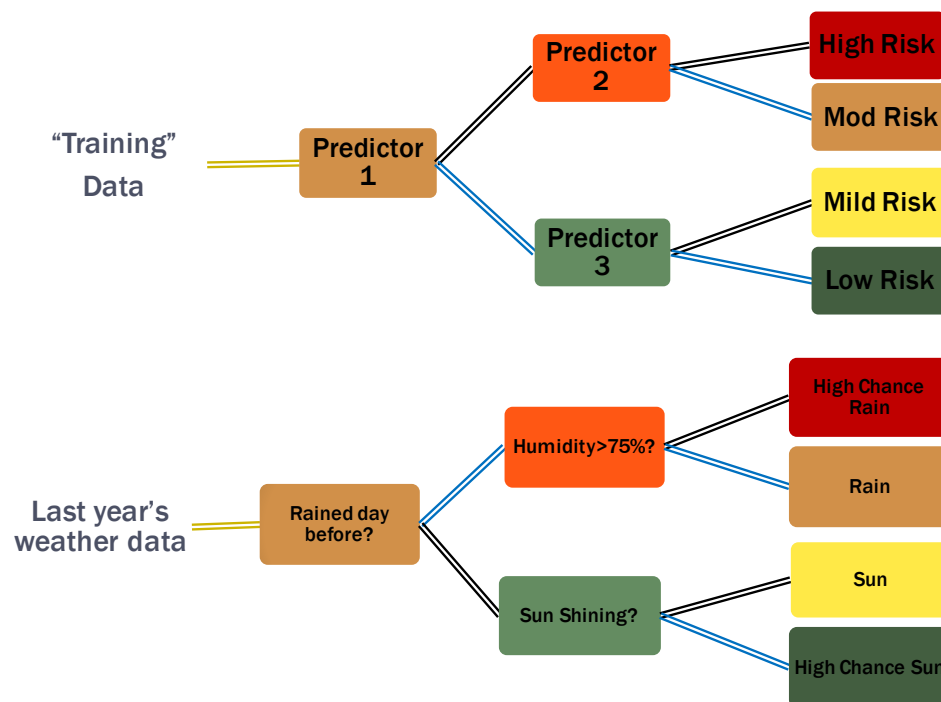
### *Binary Classification in Clinical Research: Logistic Regression and CART*

In some sense the most important distinction is a binary one: is the person suicidal or not? The most commonly used binary classification techniques in clinical research for answering such questions are logistic regression and decision trees. Reviews on their differences have been previously done but will be summarized here.

Logistic Regression is the most common statistical approach for predicting binary outcomes in clinical research. Strengths with this approach include clinician familiarity with measures like odds ratios, a numerical outcome for the weight of each variable which allows side by side risk factor comparisons, simple procedures for controlling confounds, and better classification is the true boundary between groups is linear and parallel to the predictor-outcome axes.

A less common but popular alternative modeling technique is the classification and regression tree (CART) approach, which uses recursive partitioning to deriving a decision tree (Breiman et al, 1984). Because this model repeatedly splits the dataset with predictor values to form subgroups with more “pure” classifications, it works best with data that naturally groups as a rectangle in the predictor-outcome data space. The benefits of this approach are that product can be used as a clinical algorithm for decision making without the need to do any

computation, it incorporates pruning to limit product complexity (whereas regression performs better with more predictors) and that this method performs feature selection in an automated manner. Variable selection may be more objective, which nicely counterbalances researcher-guided factor selection about questions like which elements to incorporate into multivariate adjustments. An instance below can be seen with weather data as an example.



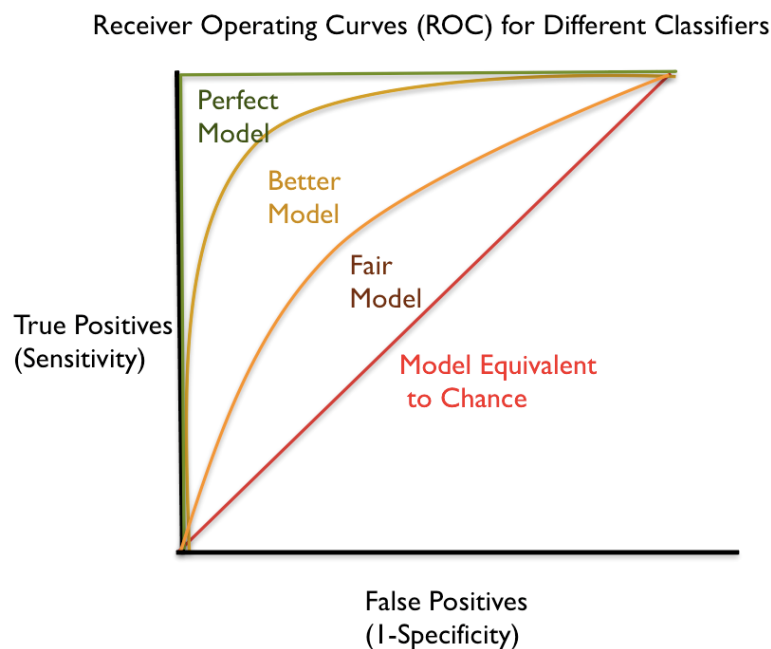
**Figure 2: Decision Trees for Classification Problems**

Branching is hierarchical, so the best available predictor will be the first to split the data, with remaining predictors used at subsequent nodes. This allows for a visual interpretation of variable predictor strength, however, it also causes construction to be suboptimal at times, as splits are “greedy”, with each split only optimizing purity of the following nodes, rather than optimizing the entire end product (Kuhn & Johnson, 2013).

### ***Receiver Operating Curves***

In most cases, there is a trade-off between sensitivity and specificity; A cut-off point that picks up more true positives will also pick up more false positives. This trade-off is commonly depicted as a Receiver Operating Curve or ROC curve, a graphical curve that shows possible outcome values for sensitivity (shown as true positives, y-axis) or specificity (shown as false positives, x-axis) given different cut-off point for classification. This curve can then be compared

to chance prediction (which forms a straight diagonal line) and be maximized by choosing the point on the curve closest to the top left. For this reason, Area Under the Curve (or AUC) of the Receiver Operating Curve is also used in cut-off point selection and model assessment: picking the model with the most top-left AUC curve. Once a model is selected based on the largest AUC, and most top left curve, a single point on the curve that is most top left is usually selected to determine the cut-point within that model which optimizes sensitivity and specificity (Mossman & Somoza, 1989).



**Figure 3: Receiver operating curve interpretation**

### *Implementation in R*

There are several ways to perform these analyses. Two examples are with the `rpart` package, which is CART-based, and the `party` package, which uses conditional inference for divisions (Therneau et al, 2010; Hothorn et al, 2006).

### *Previous applications to suicidality prediction*

Though tree-based methods originated in the field of statistical learning, and are less commonly used than logistic regression when it comes to clinical research, they have been applied to suicide prediction in the past.



A 2008 study by Mann and colleagues applied CART analysis a group of 408 high suicide risk patients with mood, schizophrenia, personality disorder. The goal was to distinguish non-attempters, remote previous attempters, and recent previous attempters from one another. This work confirmed that previous attempts are indeed the strongest risk factor for suicide. Additionally, when cost-sensitivity was incorporated (i.e. false negative were weighted more heavily than false positives), aggression emerged as the most important factor (Mann et al, 2008). The performance of this model was quite good; For the equally weighted tree, sensitivity was equal to 56%, and specificity was equal to 91%, and for the unequally weighted tree (involving aggression), there was lower sensitivity (73%), but higher specificity: sensitivity (80%).

Another high profile recursive partitioning application for suicidality prediction was employed self-harm repetition (Cooper et al, 2006). This analysis derived a rule set composed of the following four questions:

The Manchester Rule for Self-Harm Repetition (Cooper et al, 2006)

- 1) *History of Self-Harm?*
- 2) *History of Psychiatric Treatment?*
- 3) *Benzodiazepine Overdose?*
- 4) *Current Psychiatric Treatment?*

An answer of “No” to any question funnels the instance into a risk group, with later risk groups have higher chances of self-harm repetition.

The performance showed low specificity (25%) but high sensitivity (94%), but still preformed better than clinicians for risk assessment(Cooper et al, 2007).

These studies illustrate the simplicity of a decision tree as a clinical tool. They also depict the potential for uncovering unlikely risk factors and utility in ranking risk factors.

## **PART II: ORIGINAL RESEARCH**

### **Suicidal Ideation in the Epilepsy Monitoring Unit: Predictive Risk Markers and their application to Clinical tool development**

## BACKGROUND

One in 26 people in the United States will be diagnosed with epilepsy at some point in their lives, making epilepsy the 4th most common neurological disorder (England et al, 2012). For psychosocial and possibly neuropathological reasons that relate to epilepsy, people with epilepsy (PWE) also face disproportionately high rates of psychiatric comorbidity. Depression and anxiety disorders are the most common, with respective rates of 17-55% and 11-30% (Jones et al, 2005, Mendez et al, 1986, Gaitatzis et al, 2004, Jacoby et al, 1996). Psychiatric disease has established effects on both seizure-related outcomes and quality of life in general (Boylan et al, 2002, Johnson et al, 2000). Despite this, mood disorders remain under-recognized and under-treated in epilepsy care settings (Hermann et al., 2000).

A feared complication of mood disorders is self-harm and suicide. Indeed, suicide is a significant contributor to early mortality in epilepsy (Fazel et al, 2013). Though actual risk estimates differ widely, the most commonly cited values for increased risk are a 5-fold increased for PWE overall, which is further enriched to 14-fold risk in patients with psychiatric disease and epilepsy, and a 25-fold risk for patients with temporal lobe epilepsy (Harris & Barraclough, 1997, Gaitatzis et al, 2004). A meta-analysis of all studies for suicide rates in epilepsy found close to a 10-fold overall increased risk (Pompili et al, 2005).

Similar patterns can be appreciated when considering suicide attempts, self-harm, and suicidal/self-harm ideation (SSHI) (Rai et al, 2012; Hawton et al, 1980). Some studies have also found conversion rates from suicidal ideation to self-harm to be nearly 1:1 in PWE, while the figure in the general population is closer to 10:1, suggesting that placing more weight on suicidal thoughts in PWE may be warranted (Rai et al, 2012).

As with mood disorders and suicide, Self-harm behaviors and self-harm/suicidal ideation are also more common in epilepsy than in other chronic physical diseases or in control inpatients without chronic health concerns (Singhal et al, 2014; Tellez-Zenteno et al, 2007; Boylan et al, 2004; Rai et al, 2012).

Given the risks impacts on quality of life and early mortality, the high conversion rates from ideation to self-harm, and a tendency to self-poison with neurologist prescribed anti-epileptic medications (AEDs), it has been suggested that mental health be addressed in epilepsy care settings more systematically.

Appropriately, a recent clinical consensus statement put forth by the International League Against Epilepsy (ILAE) has mandated that annual depression screening using the Patient Health Questionnaire 2 (PHQ-2), which asks about depressed mood and anhedonia, should be the minimal assessment. In addition, immediate pharmacotherapy and psychotherapy should be begun due to high risk of suicide (ILAE consensus report, Kerr et al, 2011).

Even when screening is implemented, detection issues may remain as mood symptoms in PWE are often intermittent and mood disorders tend to have a “pleomorphic picture” and may not meet classical criteria set out by the DSM (Kanner et al, 2000). Mood disorders in PWE tend to present with some features of depression (depressed mood, fatigue, sleep changes), but also have unique prominent irritability, fear, labile mood, anxiety, and pain features, with a “waxing and waning” course similar to dysthymia or premenstrual dysphoric disorder (Kanner et al, 2000; Blumer et al, 2004; Kanner et al, 2006). This was first articulated in a study about the safety of sertraline treatment in PWE, which found that irritability was the chief mood symptom in over a third of depressed PWE, yet irritability is not considered a criterion for depression by the nosology of the DSM, and 71% of patients evaluated did not meet criteria for any disorder in the DSM despite having many individual mood symptoms (Kanner et al, 2000). Because this creates a gap in detection, some have advocated for the creation of a new diagnosis, such as “dysthymic disorder of epilepsy” or “interictal dysphoric disorder” (IDD), which would account for the relative lack of some symptoms (such as anhedonia), and accept new criteria (such as irritability, lability, or fear).

### ***Unmet Needs***

Given the clinical picture of depression and suicidality in epilepsy, only asking about depressed mood and anhedonia may not capture the full symptom profile of psychiatric disease in a PWE or may produce false negatives. A screen that includes all depression features and anxiety features would be most desirable, as irritability and fear are part of the anxiety screen, and a full depression screen would also capture sleep, fatigue, and suicidal ideation.

### ***Aims of this Study***

In this study, we create a clinician-independent screening task that does capture the additional emotional symptoms often associated with mood disorders in PWE with the goal of understand which, if any, are predictive for suicidal or self-harm ideation. This question would be approached in two ways: First,

through logistic regression-based odds ratios for presence of SSHI, and second, through decision tree analysis.

## **MATERIALS & METHODS**

### **Study Design**

#### ***Study Context***

This data was collected as part of the Defense Advanced Research Projects Agency's Systems Based Neurotechnology for Emerging Therapies (SUBNETS) program. This particular study followed a cross sectional survey design. This study was approved by the Ethical Board of University of California, San Francisco, with a memorandum of understanding extended to the University of California, Berkeley.

#### ***Subjects***

Fifty-six subjects were recruited from one academic, urban tertiary epilepsy care center (University of California, San Francisco Epilepsy Monitoring Unit) between the dates of July 2014 and August 2015. All patients were EMU inpatients undergoing scalp or intracranial electroencephalogram monitoring while participating in the study. The sample was 44% Male, with mean age of 27 and an age range of 20-63. Inclusion criteria for recruitment included age > 18, English fluency and literacy, ability and desire to give consent and comfort with using a touchscreen tablet for survey completion. Verbal and written consent was provided by each patient, and study participation was optional with no monetary incentive.

#### ***Data Collection Protocol and Materials***

Two survey were used in this study: The 9-item patient health questionnaire 9 (PHQ-9) and the 7-item Generalized Anxiety Disorder 7 (GAD-7) which are provided in supplementary figures 1s-3s. Both screens have been validated previously to be used in primary care settings as screening tools for depression and anxiety, respectively. The PHQ-9 has a sensitivity of 88% and a specificity of 88% at the standard cut off point (10+/27) (Kroenke et al, 2001). If the last question of the PHQ-9 is removed and the PHQ-8 is used instead, the cut-point remains the same (>10/24). The PHQ-8 has a sensitivity and specificity of 88% at this cut-point (Kroenke et al, 2009). The GAD-7 has a sensitivity of 89% and a specificity of 82% at the standard cut off point (>10/21) (Kroenke et al, 2006).

These cut-points were used to derive binary measures regarding depression and anxiety disorder diagnoses for this study. All surveys were completed using a bedside tablet (an Apple iPad air mini). Data was collected using the specially designed mood tracking application, “Moodify” in collaboration with Posit Science Brain HQ. Moodify presents sequential questions from psychiatric surveys in written form, and patients could use buttons to select symptom severity from a list of multiple choices in privacy.

## **Data Analysis**

### ***Software used:***

Data was extracted from Moodify and analyzed using R, a freely available statistical computing program (R core team, 2013). Regression analysis was performed with base R functionality. Decision tree analysis was performed using the R “party” package (Torsten et al, 2006). Final model selection was done with k-fold cross validation using the caret package (Kuhn et al, 2008).

### ***Statistical Analysis:***

In all cases, statistical significance was defined as a two-sided p-value of less than 0.05. Significance level p-values have not been corrected for multiple comparisons for two reasons: the high level of inter-correlation present in this dataset increases the likelihood of making Type II errors with the Bonferroni correction (Perneger, 1998) and probability values given as raw values may be more useful for assessing consistency between studies (Xie, 2012). Multivariate logistic regression was used to calculate demographic adjustments and seizure variable adjustments.

Study population demographics and illness factors relating to seizures and psychiatric history were characterized using descriptive statistics. Means and standard deviations are reported for continuous variables and proportions are reported for categorical variables

In order to compare likert scale items within the PHQ-9 and GAD-7 for potential risk factors for SHHI, bivariate logistic regression was performed with each item as the independent variable and Suicidal/Self-Harm Ideation as the dependent variable. To extend the potential for clinical utility as a verbal screening question, each item was dichotomized and odds ratios for SSHI were compared when experiencing the item either “half the days or more”

or “less than half the days”. Two adjustments were made by multivariate logistic regression. Adjusted odds were calculated to account for demographic factors and seizure factors known to be risk factors for suicidality.

Repeated k-fold cross validation was used for decision tree model selection. K-fold cross validation with 5 folds and 100 repetitions was used for model selection (The data was randomly split into 5 even groups, and models derived from 1 of the 5 folds were tested on the remaining 4 to ascertain performance, until each set had been a training and test set. This procedure was repeated 100 times with different splits). The best fitting model was selected among the 500 models generated on the basis of area under the curve.

In order to compare the screening metrics of the decision tree, performance was measured within sample to yield sensitivity, specificity, positive predictive value, accuracy, and diagnostic odds ratio. Equations are as described in Lo et al, 2014. In short,

$$\textit{Accuracy} = \Sigma \textit{correct predictions} / \Sigma \textit{all}$$

$$\textit{Specificity} = \Sigma \textit{true negatives} / \Sigma \textit{all}$$

$$\textit{Negative Predictive Value} = \Sigma \textit{true negatives} / \Sigma \textit{all test negatives}$$

$$\textit{Positive Predictive Value} = \Sigma \textit{true positives} / \Sigma \textit{all test positives}$$

$$\textit{Diagnostic Odds Ratio} = \textit{Positive Likelihood ratio} / \textit{Negative likelihood ratio}$$

$$\textit{Likelihood Ratio} = [\textit{True positive}/\textit{false positive}]/[\textit{True negative}/\textit{true positive}]$$

## **Definitions:**

### ***Epilepsy and Seizure Types:***

Epilepsy and Seizure Types were defined as at least two unprovoked seizures regardless of seizure type. Subclassifications for seizure type include primary generalized epilepsy, localization related epilepsy (focal) epilepsy, and psychogenic non-epileptic spells as defined by the ILAE.

### ***Irritability:***

Irritability was assessed by self-report on question 6 of the GAD-7: “*In the last two weeks, how often have you been bothered by the following problem: Feeling irritable or annoyed in the last two weeks?*”

A response of “Not at all” or “Several days” was defined as low irritability. A response of “More than half the days” or “Nearly every day” was defined as high irritability.

**Suicidal and Self Harm Ideation:** Suicidal and Self Harm Ideation (referred to simply as “Ideation”, “SSHI”, or “suicidality” in the text) was assessed by self-reported ideation on question 9 of the PHQ-9 survey: *“Over the last two weeks, how often have you been bothered by any of the following problems: thoughts that you would be better off dead, or of hurting yourself?”*

A response of “Not at all” was defined as “No self-harm ideation”. A response of “several days”, “more than half the days”, or “nearly every day” was defined as “Some self harm ideation”.

**Depression:** Depression was assessed by the accepted cut point for the PHQ-8 (sum  $\geq 10$ ), which is equivalent to the first 8 questions of the PHQ-9.

**Anxiety:** Anxiety was assessed using the GAD-7 summed score with its accepted cut point (sum  $\geq 10$ ).

## RESULTS

### Characteristics by Suicidal/Self-Harm Ideations Group

Sociodemographics, seizure factors, and psychiatric factors for the study population are shown for the whole sample population and as two groups split by presence of Suicidal/Self-Harm Ideation (SSHI) in Table 1. Differences between groups were compared using either Mann Whitney U tests or Fishers Exact Tests to test for significance.

30% of patients reported experiencing Suicidal/Self Harm Ideation in the last two weeks. In terms of demographics, they were more likely to be older, female, and unemployed, but none of these features were significantly different between groups. Patients with SSHI were significantly more likely to have focal seizures, however, other illness features such as age of seizure onset, duration of disease, number of AEDs used, and frequency of events were not significantly different between groups. Presence of any psychiatric disease, depression, or



anxiety noted in the subject chart was not significantly different between groups. Psychiatric screen values and positive outcomes were higher in subjects with SSHI, significantly so for both PHQ-9 read-outs, while only the summed score for the GAD-7 was significantly different between groups (Table 1).

### ***Prevalence of Suicidal/Self-Harm Ideation***

The prevalence of SSHI in this study sample was 30%, with 17/56 patients endorsing the last question of the PHQ-9.

### ***Age and Suicidal/Self-Harm Ideation***

The average age of the study sample was 37, with a standard deviation of 11.0 and a range of with a range of 20-63 years old. The average age of subjects with Ideation (35.5), was older than the average of subjects with no SHHI (40.5), but this difference was not significant ( $p=0.124$ ).

### ***Sex and Suicidal/Self-Harm Ideation***

As a whole, the study population has a slightly lower proportion of men than women ( 44% M, 56% F), and this proportion was mirrored in both the group with no SHHI(43% M, 56% F) and group with SHHI (47% M, 53% F) suggesting that SHHI status is not significantly associated with gender in this sample. This was confirmed by Fisher Exact test ( $p=0.778$ ).

### ***Employment and Suicidal/Self-Harm Ideation***

In this study, 30% of subjects had academic or occupational employment. Employment was higher in subjects without SSHI (35.9%) than subjects with SSHI (17%), but the difference was not significant (  $p = 0.218$  ).

### ***Seizure Factors and Suicidal/Self-Harm Ideation***

In this study, fisher's exact test indicated that distribution of diagnoses was different between groups (  $p = 0.015^*$ ). When examining each diagnosis category for differences in distributions with respect to SHHI, primary generalized epilepsy (PGE), psychogenic non-epileptic seizures (PNES), Drug resistant Epilepsy (DRE) and unknown at discharge (UNK) were not significantly different between groups. Only localization related epilepsy (focal epilepsy) was significantly different (  $p = 0.018^*$ ). Localization Related (focal) seizures were diagnosed at discharge in 45% of the study population, which accounted for 35% of the no SSH Ideation group and 71% of patients with SSH ideation group.

Age of onset of illness, number of anti-epileptic drugs(AEDs) used and frequency of seizures were all evaluated for sample mean, standard deviation and differences between groups. Each of these factors has been controversial, with inconsistent association to suicidality and mood disorders in previous studies. In this study, none of these illness-severity related features were significantly different between groups.

### ***Psychiatric History***

In order to investigate the association of psychiatric history with presence of SSHI, presence of any psychiatric history, depression history and anxiety history were each individually assessed for differences between groups. No differences were found to be significant.

### ***Psychiatric Comorbidity***

In this study population, 56% of subjects screened positive for depression and 40% of subjects screened positive for anxiety disorders based on the PHQ-8 and GAD-7, respectively. When depression and anxiety comorbidity was evaluated at the group level, the No SSHI group showed a significantly smaller proportion of patients who screen positive for depression as compared to the SSHI group (42.5% vs 88%,  $p=0.001^{**}$ ). A less pronounced trend could be appreciated with generalized anxiety disorder prevalence (31% vs 59%,  $p=0.084$ ).

## **Psychiatric Screen Items as Risk Factors for SSHI**

In order to evaluate the utility of recorded symptoms as risk factors, bivariate logistic regression was performed for every predictor with presence of SSHI as the outcome. Adjustments for confounds were also carried out for demographic factors and seizure factors. Raw, unadjusted odds ratios for SSHI were significantly elevated in groups with high symptom burden for several items, including Depressed Mood (OR=4.4, 95% CI=1.3-15.5), Appetite Changes(3.7, 1.1-12.8), Low self-esteem/Guilt (3.8, 1.2-14.2), psychomotor dysregulation (3.7,1.1-13.0), Excessive worry(3.7, 1.1-12.8), Restlessness(6.1, 1.5-27.7), and Irritability(25.0, 5.7, 179.4). Adjustment for Demographics left only Psychomotor dysregulation, Restlessness, and Irritability as significant risk factors for SSHI. On the other hand, adjustment for seizure factors indicated additional increased odds of SSHI in association with anhedonia and sleep dysregulation.

Tellingly, only high irritability, restlessness, and psychomotor changes consistently showed significantly elevated odds of SSHI across adjustments. Of these, high irritability had the largest ORs, indicating that experiencing irritability half the days or more in the last two weeks was associated with a 25-37.6 OR for concurrent suicidality ( $p \leq 0.001^{***}$  for all). Somatic signs of agitation, including psychomotor dysregulation and restlessness, showed consistent associations across comparisons, with ORs of 3.7-8.6 and 5.2-13.5, respectively. In summary, several strong and one especially striking link to SSHI could be appreciated through logistic-regression analysis of psychiatric items. Together, these features indicate an important role for emotional and somatic agitation.

It is especially interesting to consider these associations alongside the depression and anxiety diagnoses based on the summation of the PHQ-8 and the GAD-7. Only screening positive for depression was significantly associated with SHHI with an OR of 10.8(2.6-74.7). Meanwhile, screening positive for anxiety disorders was not significant despite the importance of several individual items within the screen.

## **Decision Tree Development and Testing**

In order to develop a clinical tool that emphasized feature sparsity and similarity to clinical decision making tools currently in use, we developed a decision tree using classification and regression tree (CART) analysis. The resulting optimal decision tree showed a single branch point which divided the population by their response to the irritability item: *“In the last two weeks, how often have you been bothered by becoming easily annoyed or irritable?”*. Subjects reporting no days or several days of symptoms were predicted to have no SHHI. Subjects reporting difficulty with annoyance or irritability more than half the days or nearly everyday were predicted to be positive for SHHI.

This simple tree accurately predicted SSHI status in 45/56 patients, or 80.4% of the time. This corresponds to a misclassification rate of 19.6%, with a sensitivity of 88.2%, and a specificity of 77%. The negative predictive value of this algorithm was 94%. In other words, of the 32 subjects with low irritability predicted to have no SHHI, only 2 subjects were falsely classified. With a positive predictive value of 62%, there were more false positives (9/39), than

false negatives (2/17).

### **Irritability, Depression, and Focal Epilepsy as Classifiers**

Group classification by irritability symptomology outperformed classification by both depression and focal epilepsy, which together represent the two most considered risk factors in the general population and in epilepsy, respectively. Metrics included statistical features (accuracy, sensitivity, specificity, negative predictive value, and positive predictive value) and practical features (assessment materials needed and the potential for screening without a clinician). Metrics were uniformly more favorable for irritability-based assessment, with only one exception. Classification by focal epilepsy demonstrated a higher specificity (84% vs 77%) and positive predictive value (67% vs 62%) than irritability, while irritability outperformed focal epilepsy on the remaining measures including having fewer false negatives (71% vs 94% ruled out correctly). Despite being 8 questions instead of 1, the PHQ-8 performed worse on almost every measure as compared to irritability. It showed lower accuracy (68%), lower specificity (59%) and lower negative and positive predictive value (92%, 50%). The one exception was the sensitivity of depression based screening, which was high and equivalent to Irritability'.

### **LIMITATIONS**

The largest barrier to analysis in this pilot study was a sample size (N=56). In light of this, we limited the number of predictors in multivariate adjustment of logistic regression to no more than 3 covariates for all adjustments, and all values were reported as univariate odds ratios in addition to adjusted odds ratios. Furthermore, our small sample size limited our ability to test the final decision tree with new data for this study. Lastly, this data was collected in a single, academic tertiary epilepsy care center with an extremely high burden of psychiatric disease. Though this is the most high-needs setting for implementation of psychiatric screening, our findings may not be applicable for patient samples with better seizure control and fewer psychosocial challenges (such as community based samples) or samples coming from outside of this urban, united states bay area.

One additional limitation pertains to our data collection. Currently, specific surveys exist for both irritability and suicidal ideation, and objective measures could have been made to remove self-report from the design. Though other tools could have had been superior in terms of validation and objectivity, the benefit of choosing to use self-report from common surveys currently used in primary care is the boost in potential clinical utility.

Last of all, and most importantly, though our aim was to create a tool that can screen for suicidal and self harm ideation, the intent has always been to use it for choosing who to engage in further assessment. Either a neurological or a mental health care provider would further assess suicidal ideation, suicidal intent and plan and infer the risk to self or others. The conclusions and tool created in this work should not serve as replacement for mental health screening and care.

## **DISCUSSION**

Even in a study that was not aiming to evaluate psychiatric burden, the prevalence of mood disorders is striking. More than half (56%) of the sample screen positive for depression, and 40% screened positive for generalized anxiety disorder.

Similarly, nearly 1/3 of patients reported some suicidal ideation in the last two weeks. This number is incredibly high when compared to other depressed patient groups. For instance, only 10% of patients followed by primary care physicians and outpatient psychiatrists for depression have suicidal and self harm ideation as measured by the same question (Simon et al, 2013). However, if compared to prior estimates in patients with epilepsy, it is not remarkable; A large, population-based analysis done in Canada shows a prevalence of 25% in a mostly outpatient sample (Tellez- Zenteno et al, 2007).

Interestingly, within our study, demographics, seizure factors, and psychiatric history self-reported by the patient proved to be of little distinguishing value. Only focal epilepsy was found to be significantly different in patients with suicidal ideation as compared to those without. Our study not only qualitatively replicates the most significant psychiatric risk factor in epilepsy, but also replicates it quantitatively .

Though demographic risk factors are important to recognize, understanding modifiable risk factors has the additional benefit of serving as an intervention point, making analysis about psychiatric symptom items most relevant. Several psychiatric screen-based items were shown to be significantly enriched in patients with SSHI. Significantly elevated unadjusted odds ratios included depressed mood, appetite changes, guilt, psychomotor changes, excessive worry, restlessness and irritability (Table 2), of which irritability, restlessness, and psychomotor agitation showed the most consistent significance, even with adjustment for demographics and factors related to epilepsy.

There were several surprising elements to the screen results. First, the preponderance and importance of anxiety-related individual symptoms, despite a lack of significance for the anxiety screen overall indicates that item-level analysis is crucial for understanding this particular patient population. Highlighting the importance of depression over anxiety as an associated feature for SHHI would completely miss the most important risk factor derived from individual analysis, irritability. This may be one reason why irritability has not previously been established as a standard item in suicide risk assessment, though it may only be this relevant for PWE. Furthermore, the constellation of symptoms that was significant across adjustments was remarkable because of its clinical consistency. Together, irritability, restlessness, and psychomotor agitation paint a cohesive and novel clinical picture characterized by both physical and emotional agitation which has already been a topic for discussion for researchers and clinicians interested in mood disorders in epilepsy.

Of these highlighted risk factors, irritability undeniably represents the largest and most significant risk factor, with an odds ratio of 25-37.6 (depending on the adjustment) and a consistent significance of  $p < 0.001$ . Only overall depression (quantified by 8 questions) comes close to so strongly and consistently being associated to suicidal ideation in this study. However, depression is appropriately widely recognized in the suicide research community and by clinicians, whereas irritability is not similarly weighted in the literature or clinically. This new knowledge may provide valuable insight.

For a more quantitative approach, this study provides both a decision making algorithm and a single, simple question that may be applied to clinical assessment: “*Have you felt irritable or annoyed on half the days or more the last two weeks?*”. Notably, this question is likely to be less stigmatizing than asking

about depressed mood or suicidal behavior or thoughts because there is no popularized association with psychopathology as there may be with asking about depressed mood for instance. This question may also provide a transition point for a medical provider to dive into further screening using conventional questions about suicidal ideation, intent, plan, and risk to self and to others.

Another concern that may be addressed with this approach is suicidality concealment. This question may help infer suicidality status without asking directly, though further screening would need to follow. This could be especially relevant for emergency departments that receive PWE after self-poisoning.

Because most similar studies have analyzed depression and anxiety contributions at the level of the scale rather than item level, it may be the case that this is a broad finding, but has not previously been detected or highlighted because it was overlooked. This is especially noteworthy given the superior performance of irritability over depression-based screening and focal epilepsy-based screening (Table 3), which represent the most well accepted risk factors from the general population and the epilepsy population, respectively. A single irritability question's diagnostics odds ratio (OR=25.5) was almost twice that of 8 questions summed to capture Depression (OR=10.8) and five times higher than the diagnostic odds of focal epilepsy (OR=4.8), the most widely accepted risk within epilepsy populations. These findings, confirmed by both logistic regression with various adjustments and decision tree analysis, are especially significant given the current lack of irritability screening in either general or epilepsy based psychiatric screening.

This work resonates strongly with much of the efforts previously made to create an epilepsy-specific mood disorder (Kanner & Barry, 2001). It is now clear that missing irritability could not only cause false negative assessments in mood disorders, but it could also miss suicidality. Conversely, understanding why irritability and annoyance are so important for suicidality in PWE will likely lead to a better understanding of mood in epilepsy too, as that is also marked by increased irritability and lability (Kanner et al, 2000, Blumer et al, 2004).

Though these previous paths of research may suggest that irritability is an epilepsy-specific risk factor, there are also insights that may suggest otherwise. For instance, irritability is a common thread that connects many other high suicide risk conditions, including bipolar disorder

borderline personality disorder, alcohol dependency, attention deficit hyperactive disorder, and adolescence (Benazzi & Akiskal, 2005, Stone et al, 1988;Wojnar et al, 2009; Hinshaw, 2012; Dougherty et al, 2009). When the term “irritability” is not specifically used, similar conceptualizations such as “reactive aggression” or “impulsivity” are applied, and these terms are likely to be highly inter-related. Interestingly, AEDs are used as mood-stabilizers in borderline disorder and bipolar disorder, potentially hinting at shared pathophysiology for neural and emotional disinhibition. Further work must be done to fully understand the operational meanings, however, it is possible that the tools developed in this study have even broader application in other disorders.



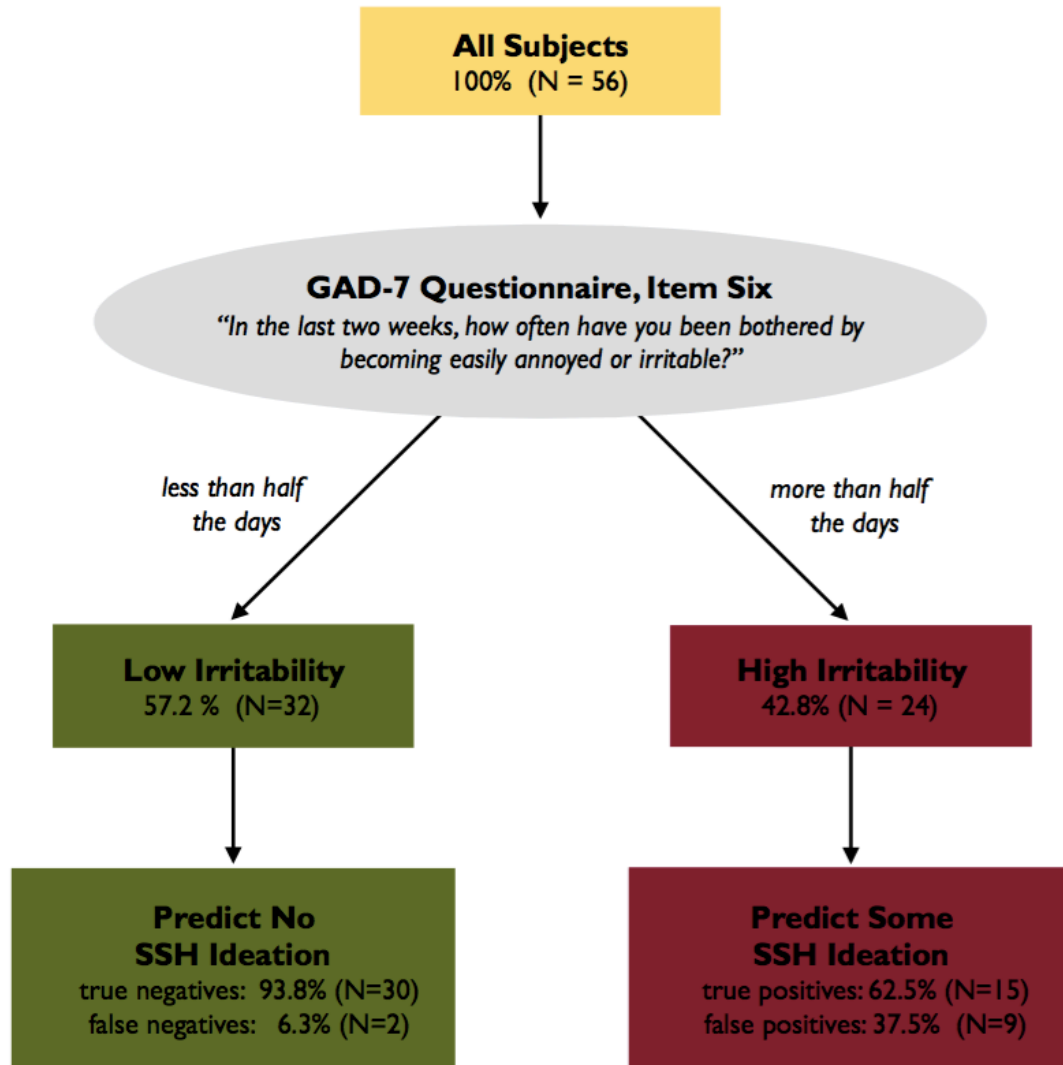
## TABLES AND FIGURES

**Table 1: Sample Characteristics for the Population and by Ideation Group.** Overall, 30% of patients were experiencing Suicidal/Self Harm Ideation. In terms of demographics, they were more likely to be Older, Female, and Unemployed, but none of these features were significantly different between groups. Patients with SSHI significantly were more likely to have focal seizures, however, other illness features such as age of seizure onset, duration of disease, number of AEDs used, and frequency of events were not significantly different between groups. Presence of any psychiatric disease, depression, or anxiety noted in the subject chart was not significantly different between groups. Psychiatric screen values and positive outcomes were higher in subjects with SSHI, significantly so for both PHQ-9 read-outs, but only the summed score for the GAD-7.

Population Characteristic	All Subjects	No SSHI	SSHI	p-value <sup>Test</sup>
Sample Size	N= 56 (100%)	N= 39 (70%)	N= 17 (30%)	-----
<b>Demographic Characteristics</b>				
Age	37(10.98)	35.5(10.44)	40.5(11.7)	p = 0.12 <sup>MWU</sup>
Male Gender	25 (44%)	17(68%)	8 (32%)	p = 0.78 <sup>FTE</sup>
Employment	30%	35.9(14)	3 (18%)	p = 0.22 <sup>FET</sup>
<b>Seizure Factors</b>				
Seizure Type Diagnosis at Discharge				
<i>Primary Generalized Seizures</i>	6 (10.5%)	4 (10%)	2 (12%)	p = 0.71 <sup>FET</sup>
<i>Localization-Related (Focal) Seizures</i>	26 (45.5%)	14 (35%)	12 (71%)	p = 0.02 <sup>*FET</sup>
<i>Psychogenic Non-Epileptic Seizures</i>	9 (16%)	6 (15%)	3 (18%)	p = 0.73 <sup>FET</sup>
<i>Drug Resistant Epilepsy</i>	13 (23%)	13 (32.5%)	0 (0%)	p = 0.16 <sup>FET</sup>
<i>Unknown at Discharge</i>	3 (5%)	3 (7.5%)	0 (0%)	p = 0.55 <sup>FET</sup>
Age at Onset (years)	23.43 (14.4)	22.54(14.32)	25.5 (14.8)	p = 0.61 <sup>MWU</sup>
Duration of disease (years)	13.67 (11.4)	13.09(11.48)	15 (11.4)	p = 0.42 <sup>MWU</sup>
Number of AEDs used	2.05 (1.1)	1.95(0.849)	2.3 (1.1)	p = 0.33 <sup>MWU</sup>
Frequency of events				
<i>less than monthly</i>	7 (13%)	4 (10%)	3 (18%)	p = 0.67 <sup>FET</sup>
<i>monthly up to weekly</i>	17 (30%)	13 (32%)	4 (24%)	p = 0.54 <sup>FET</sup>
<i>weekly up to daily</i>	20 (34%)	12 (30%)	8 (47%)	p = 0.36 <sup>FET</sup>
<i>daily or greater</i>	11(19.6%)	9 (23%)	2 (12%)	p = 0.47 <sup>FET</sup>
<b>Self Reported Psychiatric history</b>				
Any history	22 (39%)	14 (36%)	8 (47%)	p = 0.55 <sup>FET</sup>
Depressive Disorders	19 (34%)	28 (72%)	8 (47%)	p = 0.22 <sup>FET</sup>
Anxiety Disorders	15 (27%)	28 (72%)	4 (24%)	p = 1.00 <sup>FET</sup>
<b>Current Psychiatric Comorbidity</b>				
PHQ-9 Summed Score	10.8 (6.26)	8.9 (5.6)	14.9 (5.8)	p = 0.001 <sup>** MWU</sup>
Screen + for Depressive Disorders	32 ( 56 %)	17 (42.5%)	15 (88%)	p = 0.001 <sup>** FET</sup>
GAD-7 Summed Score	9.2 (5.7)	7.8 (5.4)	12.4 (5.4)	p = 0.005 <sup>** MWU</sup>
Screen Positive for Anxiety Disorders	23 ( 40%)	13 (31%)	10 (59%)	p = 0.08 <sup>FET</sup>
<b>SSHI= Self-Harm / Suicidal Ideation</b>			<b>MWU = Mann Whitney U Test</b>	
<b>Note: Values may not sum to 100% due to rounding</b>			<b>FET = Fisher's exact test</b>	
<b>* p &lt; 0.05, ** p &lt;0.01, *** p &lt;0.001</b>			<b>Units: N(%) or Mean(SD)</b>	

**Table 2: Psychiatric Screen Odds Ratios for presence of Suicidal/Self-Harm Ideation.** Each psychiatric screen item was dichotomized for simplicity of interpretation. All item Odds are for patients experiencing the symptom on more than half the days as compared to less than half the days. The summed screen used in diagnosis was also dichotomized to meeting criteria for depression or not. Odds given represent screening in for the disorder. Though many individual items showed significant odds ratios, only psychomotor changes, restlessness, and irritability were significant in unadjusted bivariate logistic regression and adjusted multivariate logistic regression.

Psychiatric Screen Items	Unadjusted Bivariate Odds		Odds Adjusted for Demographic Factors <sup>‡</sup>		Odds Adjusted for Seizure Factors <sup>‡</sup>	
	OR	95% CI	OR	95% CI	OR	95% CI
<b>Depressive Disorder Items</b>						
Q1: Loss of interest (Anhedonia)	3.2	1.0 10.9	2.8	0.8 10.1	5.8 *	1.5 30.2
Q2: Depressed mood	4.4 *	1.3 15.5	3.1	0.8 13.5	5.2 *	1.4 22.6
Q3: Sleep dysregulation	1.3	0.4 4.1	0.8	0.2 3.2	4.5 *	1.2 19.8
Q4: Low Energy (Anergia)	3.5	1.0 12.7	3.7	0.9 18.4	1.6	0.5 6.0
Q5: Appetite changes	3.7 *	1.1 12.8	3.2	0.9 11.8	6.1 *	1.5 30.3
Q6: Low self-image, Guilt	3.8 *	1.2 14.2	3.3	1.0 13.1	3.5	1.0 14.1
Q7: Concentration changes	1.8	0.6 6.1	1.5	0.4 6.0	2.3	0.6 8.8
<b>Q8: Psychomotor changes</b>	<b>3.7 *</b>	<b>1.1 13.0</b>	<b>4.4 *</b>	<b>1.1 19.9</b>	<b>8.6 *</b>	<b>1.9 62.5</b>
<b>Screened in for Depressive Disorder<sup>°</sup></b>	<b>10.8 **</b>	<b>2.6 74.7</b>	<b>16.2 **</b>	<b>2.9 153.6</b>	<b>13.0 **</b>	<b>2.7 104.7</b>
<b>Anxiety Disorder Items</b>						
Q1: Anxious mood	2.6	0.8 8.5	2.3	0.7 8.9	2.4	0.7 8.8
Q2: Uncontrolled worry	1.8	0.6 5.8	1.4	0.4 4.8	3.2	0.9 12.2
Q3: Excessive worry	3.7 *	1.1 12.8	3.4	1.0 12.5	1.9	0.5 6.7
Q4: Difficulty relaxing	2.4	0.7 8.1	1.7	0.5 6.4	3.1	0.8 12.7
<b>Q5: Restlessness</b>	<b>6.1 *</b>	<b>1.5 27.7</b>	<b>5.2 *</b>	<b>1.1 28.3</b>	<b>13. **</b>	<b>2.4 124.6</b>
<b>Q6: Irritability</b>	<b>25.0 ***</b>	<b>5.7 179.4</b>	<b>37.6 ***</b>	<b>6.5 441.9</b>	<b>25.5 ***</b>	<b>5.2 219.1</b>
Q7: Fearful dread	2.3	0.7 7.5	2.4	0.7 8.4	2.5	0.7 9.6
Screened in for Anxiety Disorder <sup>Δ</sup>	2.9	0.9 9.6	2.2	0.6 8.3	2.9	0.8 11.4
<sup>°</sup> Positive for Depression if PHQ-8 sum ≥ 10 <sup>Δ</sup> Positive for Anxiety if GAD-7 sum ≥ 10		* p < 0.05 , ** p < 0.01 , *** p < 0.001, <b>Bold Text:</b> significant across all adjustments		<sup>‡</sup> Demographic Factors: Age, Sex, Employment <sup>‡</sup> Seizure Factors: Focal Epilepsy, Number of Anti-Epileptic Drugs, Seizure Frequency		



**Figure 1: Decision Tree Based Prediction of Ideation** Classification and regression tree derived model for suicidal / self-harm (SSH) ideation prediction shows a single split on Irritability with a cut-point corresponding to experiencing symptoms half the days in the last two weeks

**Table 3: Metrics for Irritability and Traditional Risk Factors.** Statistical and Practical Metrics for High Irritability, Screening positive for Depression, and a diagnosis of Focal Epilepsy as diagnostic measures for Suicidal & Self Harm Ideation

Screening Metrics	Irritability <sup>I</sup>	Depression <sup>D</sup>	Focal <sup>F</sup>
Diagnostic Odds Ratio	25.0	10.8	4.8
Accuracy	80 %	68%	68%
Sensitivity	88 %	88 %	48%
Specificity	77 %	59%	84%
Negative Predictive Value	94 %	92%	71%
Positive Predictive Value	62%	50 %	67%
Assessment Materials	1 Question	8 Questions	EEG/history
Clinician Independent?	Yes	Yes	No
* LR = Likelihood Ratio D : By Summed PHQ-8 $\geq 10$		I : High Irritability by item 6 of GAD-7 $\geq 2$ F : Localization related (focal) epilepsy	

## SUPPLEMENTARY MATERIALS

### PHQ - 9

Name \_\_\_\_\_ Date \_\_\_\_\_

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

(For office coding: Total Score \_\_\_\_ = \_\_\_\_ + \_\_\_\_ + \_\_\_\_)

**Figure 1s : Paper form of the Patient Health Questionnaire – 9**

*Reproduced from Spitzer et al, 1999*

### GAD-7

Over the <i>last 2 weeks</i> , how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score \_\_\_\_ = Add Columns \_\_\_\_ + \_\_\_\_ + \_\_\_\_

**Figure 2s: Paper Form of the Generalized Anxiety Disorder – 7**

*Reproduced from Spitzer et al, 2006*

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