Life in the Fast Lane: Rapidly Acting Agents
Acute Care Research

Cheryl McCullumsmith, MD PhD
Disclosures

Consultant, Advisory Board  Janssen
Grants :American Foundation for Suicide Prevention
Janssen
Allergan
Acute Care Research

Determining which treatments help patients in life threatening crises
Chest Pain

Where do you go?

What happens in ED?

What workup happens?

What information will you leave with/what followup?

<table>
<thead>
<tr>
<th>Rank</th>
<th>Ages 18–65</th>
<th>Rank</th>
<th>Ages 18–65</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Malignant Neoplasms 184,190</td>
<td>6</td>
<td>Cerebrovascular 21,093</td>
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<tr>
<td>2</td>
<td>Heart Disease 126,738</td>
<td>7</td>
<td>Chronic Lower Respiratory Disease 20,231</td>
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<tr>
<td>3</td>
<td>Unintentional Injury 78,327</td>
<td>8</td>
<td>Liver Disease 19,796</td>
</tr>
<tr>
<td>4</td>
<td><strong>Suicide</strong> 28,628</td>
<td>9</td>
<td>Homicide 15,627</td>
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<tr>
<td>5</td>
<td>Diabetes Mellitus 21,143</td>
<td>10</td>
<td>HIV 10,770</td>
</tr>
</tbody>
</table>

*Data courtesy of CDC*
Suicidal ideation and behavior are one of the main psychiatric complaints in the ER

- Patients are admitted primarily for safety
- Released after 5-7 days before medications begin to truly work
- Few chronic psychiatric medications have demonstrated efficacy in treating suicidality (lithium, clozapine)
- No medications have demonstrated efficacy in treatment of acute suicidality
PROBLEMS IN PREVENTION OF SUICIDE:

Identification of those at risk

Provision of appropriate level of care in an appropriate time frame

Treatments that are specific, rapid and effective
Risk factors for suicide

- Previous attempts
  - but many deaths happen on first attempt
- Psychiatric Illness—especially mood disorders
  - ALL psychiatric illnesses increase risk
  - 90% have diagnosable illness at time of death
- Drug use—especially alcohol and cocaine
- Social stressors: divorce, loss of job, financial stress, social isolation
- Hopelessness, impulsivity
- White Men, older
- Family History
- Chronic Medical illness, especially CNS
Epidemiology
Risk Factors

Population Risk

Not Risk for an Individual
Identification of those at Risk

Heart Attack

- Chest Pain
- “How do you feel”
- Lab work, vitals, EKG,
- Invasive tests, monitoring
- Specific Diagnosis and Underlying Diagnoses
- Specific Treatment

Suicide

- Suicidal Ideation
- “How do you feel”
- “How do you feel now”
- “How do you feel now”
- Underlying Diagnosis
- Treatment of Underlying condition
Assessing suicide risk

1. Ask

   “Have things gotten so bad lately that you’ve wished you just weren’t here”
   “Have you felt like you might do something to harm yourself”
   Ask about access to means: GUNS

2. Look at the overall picture

   Don’t lose the forest for the trees
   Look at past behavior, risk factors

3. Get collateral information:

   We are not human lie detectors
Scales prospectively associated with suicide behavior

- Beck Hopelessness Scale
  - Questions on hopelessness
- Barrett Impulsivity Scale
- Aggression Scale
- Perceived Social Support Scale
- Perceived Stress Scale
Past behavior predicts future behavior... but will not change

• Suicide Intent

• Suicide Intent Scale-Worst

• Suicide Behaviors Questionnaire
Can we put all of this together?
Suicidal Ideation

Depression

Impulsivity

Suicide Attempt

Lack of Coping Skills

Death by Suicide

Hopelessness
Hopelessness risks

- Depression
- Impulsivity
- Suicidal Ideation
- Suicide Attempt
- Death by Suicide

Factors:
- Lack of Coping Skills
- <HS education
- Physical Illness
- Unstable Housing
- Unstable Employment
- Traumatic Life Events
- Lack of Social Support

UTMC

This diagram illustrates the relationship between hopelessness and various risk factors, leading to suicidal ideation, suicide attempt, and death by suicide.
Impulsivity risks

- Depression
- Impulsivity
- Hopelessness
- Suicidal Ideation
- Suicide Attempt
- Completed Suicide

Factors:
- Physical/Sexual abuse
- Cocaine
- Mania Psychosis
- Aggressive
- Violent offense
- Lack of Coping Skills
Depression risks

- Depression
  - Impulsivity
  - No treatment
  - Alcohol
  - Physical/Sexual abuse
  - Mania
  - Psychosis
- Suicide Ideation
  - No/poor insurance
- Suicide Attempt
  - Lack of Coping Skills
  - Death by Suicide
- Hopelessness
  - Female
  - White
UTMC

Suicidal Ideation
Suicide Attempt
Completed Suicide

Depression
Impulsivity

No treatment
No/poor insurance

Lack of Social Support
Lack of Coping Skills

Hopelessness

Suicide

Physical Illness
Unstable Housing

<HS education
Unstable Employment

Male

Access to Lethal Means

Alcohol
Cocaine

Physical/Sexual abuse
Mania Psychosis

Aggressive
Violent offense

No treatment

Factor to be addressed by Brief Intervention--DBT
Factor to be addressed by Referral to Treatment--Individualized

Female

White

Education

Lack of Social Support

Unstable Housing

Traumatic Life Events

Violent offense

Unstable Employment

<HS education

Access to Lethal Means

Hopelessness

Cocaine

Physical/Sexual abuse
Mania Psychosis

Aggressive
Violent offense

No treatment

Factor to be addressed by Brief Intervention--DBT
Factor to be addressed by Referral to Treatment--Individualized
CAN WE DO A BETTER JOB IDENTIFYING?

Better questions

Objective Measures
Goal: Ideal Assessment

• **Proxy** for suicide (predicts prospectively)
• **Quantitative** with clinical meaning
• **ReACTIVE to rapid changes**
  – also to slower changing factors
  – considers overall risk
• **Characterizes dimensions**
  – (ie arrhythmia vs blocked artery)
  – Impulsive / coping skills vs ruminative
Where to go from here?

SIBAT Suicidal Ideation and Behavior Assessment Tool

• Evidence based: what has actually been shown to predict suicidal behavior prospectively

• Converges on our newer understanding of suicidal behavior

• Addresses our newer understanding of the rapidity with which suicidal ideation can change
Objective Measures
Identification of Suicidal Patients with Machine Learning Recognition of Auditory and Linguistic Characteristics

Brian Connolly
John Pestian
Acoustic Features and Suicidal Ideation

- **prasody**
  - Fundamental frequency $F_0$
  - Rate of vocal fold vibrations
  - Range and Average affected

- **rate**
  - Pause Duration
  - Speech rate

- **volume**
  - energy
# Ubiquitous Questions Responses

<table>
<thead>
<tr>
<th></th>
<th>Suicidal</th>
<th>Mentally Ill</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laughed during interview</td>
<td>39.4 %</td>
<td>69.1%</td>
<td>71.9 %</td>
</tr>
<tr>
<td>“No” to “Are you angry?”</td>
<td>47.2</td>
<td>67.5</td>
<td>86</td>
</tr>
<tr>
<td>Laughed to anger question</td>
<td>12.6</td>
<td>35</td>
<td>41.3</td>
</tr>
<tr>
<td>Sighed during the interview</td>
<td>14.2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>“No” to “Do you hurt emotionally?”</td>
<td>40.9</td>
<td>66.7</td>
<td>70.2</td>
</tr>
<tr>
<td>“Hope” to “Do you have hope?”</td>
<td>48</td>
<td>72.4</td>
<td>75.2</td>
</tr>
</tbody>
</table>
Study Design

• Machine based learning algorithms were used to sort patients by common linguistic and auditory characteristics

• Throw all the subjects into one big pile....

• The algorithms can separate suicidal patients in PES from nonsuicidal patients in PES

• **Goal**: real time assessment of risk while talking to pt
Project #2:
EEG changes in Suicidal Patients

Nasrin Shahana
Elana Harris MD PhD
PROBLEMS IN PREVENTION OF SUICIDE:

Identification of those at risk

Provision of appropriate level of care in an appropriate time frame

Treatments that are specific, rapid and effective
Appropriate Level of Care in an Appropriate Time Frame

Heart Attack
- Chest Pain
- Inpatient
- Observation
- Cardiologist
- Primary Care Physician

Suicide
- Suicidal Ideation
- Inpatient
- ---
WHAT HAPPENS IF YOU ARE IN CRISIS BUT DON’T NEED HOSPITALIZATION?
Outcomes research

Development of a Novel Patient-Centered Monitoring Strategy to Improve Patient Outcomes after Psychiatric Crisis

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1. Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH

Background
Quantifying treatment success in psychiatry has been hindered by heavy reliance on subjective provider assessments. Patient-centered and standard quality metrics are critical missing components of both routine clinical work and program evaluation. This project developed an innovative monitoring strategy to improve outcomes after psychiatric crisis using both traditional psychiatric measures and adaptive utilization of electronic health records (EHR) and is anchored by patient-centered, patient-driven goals and feedback.

Methods
This multi-modal, patient-centered approach was modeled in the STEDI (Stabilization, Treatment, Evaluation, and Disposition) clinic, which transitions patients from psychiatric crisis to permanent outpatient care. Each STEDI clinic session began with standardized depression and anxiety scales. Information was also integrated from the EHR, providing ongoing insight into the patient's evolving condition including medication status, medical illness, emergency room visits, and re-hospitalizations. Finally, the core assessment focused on patient driven goals and complete evaluation of needs and gaps in understanding using a Patient Understanding of Care Questionnaire. These assessments provided the basis for all treatment decisions.

Results
The following patient case illustrates the efficacy of this monitoring strategy. Ms. S., a 65 y.o. woman with bipolar II disorder, was referred to STEDI clinic after a 7 day hospitalization for homicidal ideation and mixed mood symptoms.

- Traditional Psychiatric Assessment: PHQ-9 score of X and GAD7 score of X indicated persistently high irritability and anxiety post-discharge. Ms. S's Depakote was increased as a result.
- EHR review: Ms. S. had an emergency room visit 1 week after discharge that she did not disclose to the STEDI clinic provider. At the next STEDI apt discussed treatment plan and medical follow-up.
- Patient Goals and Needs Assessments: Ms. S. has significant stress due to transportation barriers and guardianship of her granddaughter. She was given options to follow-up at a facility closer to her home. Patient was also provided information regarding online and in-person support groups to talk about her granddaughter and other issues.

Utilizing the monitoring strategy treatment was centered around the patient's main goal of reducing her homicidal thoughts and maintaining positive family relationships.

Discussion
This novel monitoring strategy consisting of standardized patient evaluations, EHR mining, and patient-centered metrics creates a comprehensive approach to adaptive patient driven care after psychiatric crisis.
STEDI Clinics
STEDI clinic flow

1. **Is the patient STEDI clinic eligible?**
   - **Yes:**
     - Complete intake form
     - Make appointment via social worker for 1-2 days post-discharge
     - Patient discharged with STEDI clinic packet
   - **No:**
     - Call, evaluate and reschedule appointment

2. **PES/INPATIENT DISCHARGE**
   - **YES:**
     - Patient sees STEDI clinic prescriber
     - Patient continues to see social worker
   - **NO:**
     - Patient discharged once outpatient psychiatric plan is established

3. **STEDI CLINIC**
   - Social worker assessment:
     - Meds, transportation, MSE, DBT, goals assessment
   - **YES:**
     - Did the patient arrive at their first STEDI clinic appointment?
       - **YES:**
         - Call, evaluate and reschedule appointment
       - **NO:**
         - Contact Mobile crisis
   - **NO:**
     - Patient continues to see social worker

4. **REFERRAL**
   - **YES:**
     - Complete intake form
   - **NO:**
     - Make appointment via social worker for 1-2 days post-discharge

5. **TRANSITION TO OUTPATIENT**
   - **YES:**
     - Patient sees STEDI clinic prescriber
   - **NO:**
     - Patient discharged once outpatient psychiatric plan is established

6. **Evaluation Disposition**
   - **YES:**
     - Patient sees STEDI clinic prescriber
   - **NO:**
     - Patient continues to see social worker

7. **Stabilization Treatment**
   - **YES:**
     - Patient sees STEDI clinic prescriber
   - **NO:**
     - Patient continues to see social worker
Figure 1. All consumers represented above were offered follow-up appointments in the transitional psychiatric clinic (TPC) within 3 days (green lines, n = 69) or within 4-14 days (blue lines, n = 315). Subjects offered follow-up in the TPC within 3 days had a significant delay in returning to the emergency department (ED) for psychiatric, but not medical crisis, highlighting the effectiveness of rapid outpatient psychiatric follow-up for consumers seen in the ED.
PROBLEMS IN PREVENTION OF SUICIDE:

Identification of those at risk

Provision of appropriate level of care in an appropriate time frame

Treatments that are specific, rapid and effective
Specific Treatments

Heart Attack
- Chest Pain
- Arrhythmia --- pacer or drug
- Blockage – drug or stent
- Muscle problem : LVAD, txp

Suicide
- Suicidal Ideation
- --- treat depression
- --- treat substance use disorder
- -- treat anxiety, psychosis, etc
Antidepressants and Depression

• STAR*D: 37% remission after optimized dose of citalopram for 12 weeks

• Co-MED trials: compared antidepressant combination therapies to SSRI monotherapy and found 38% remission at 12 weeks 39% at 7 months
Antidepressants and Suicide Risk

• Leon et al. 2011:
  – Looked at 757 pts over up to 27 years
  – Antidepressant treatment associated with lower rates of suicidal behavior

• Erlangson and Conwell 2014
  – Geriatric patients who filled antidepressant rx had significantly lower suicide rates
  – 2% and 3% decline in the rate for men and women, respectively, considered in treatment with antidepressants, with each additional year of age.
Suicidality Treatments: Lithium Maintenance

Rates per 100 people years

- No Lithium
- Lithium
- Gen Pop

- Baldessarini et al.
- 2003

- Total Acts: 3.1, 0.2, 0.3
- Attempts: 4.7, 0.3, 0.9
- Suicides: 0.9, 0.2
CLOZAPINE

Meltzer et al.,[95] with permission from the Archives of General Psychiatry.

\[ p = 0.02 \]

<table>
<thead>
<tr>
<th>Day</th>
<th>0</th>
<th>70</th>
<th>182</th>
<th>378</th>
<th>574</th>
<th>742</th>
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<tbody>
<tr>
<td>Clozapine cumulative events (no.)</td>
<td>0</td>
<td>43</td>
<td>69</td>
<td>91</td>
<td>100</td>
<td>102</td>
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<tr>
<td>Clozapine at risk (no.)</td>
<td>490</td>
<td>393</td>
<td>346</td>
<td>308</td>
<td>277</td>
<td>35</td>
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<tr>
<td>Olanzapine cumulative events (no.)</td>
<td>0</td>
<td>50</td>
<td>81</td>
<td>112</td>
<td>128</td>
<td>141</td>
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<tr>
<td>Olanzapine at risk (no.)</td>
<td>490</td>
<td>410</td>
<td>365</td>
<td>312</td>
<td>269</td>
<td>39</td>
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Clinically Meaningful Change in a Clinically Meaningful Timeframe
RAPIDLY ACTING ANTIDEPRESSANTS
Subanaesthetic Ketamine Produces an Acute Antidepressant Response


<table>
<thead>
<tr>
<th>Week1</th>
<th>Week 2</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>Ketamine</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

0.5 mg/kg IV Infusion
N=7 subjects
Summary: ketamine efficacy on depression

- Coyle & Laws, 2015
- Lee et al. 2015
- Romeo et al. 2015
- McGirr et al. 2015
- Fond et al. 2014
- Romeo et al. 2015
- Lee et al. 2015
- Romeo et al. 2015

Favors ketamine

Favors control

Standard mean difference (SMD)

24 hours
24 hours
24 hours
24 hours
3-4 days
7 days
7 days
Side effects

- Dissociative feelings
- Hallucinations, dysphoria, anxiety, flashbacks
- Elevated pulse and BP
- Elevated RR
- Nausea/vomiting, increased muscle tone, anaphylaxis, rash, increased IOP
Ketamine for Suicidal Ideation
Many studies have shown acute decrease in suicidal ideation after ketamine infusion

<table>
<thead>
<tr>
<th>Author and Title</th>
<th>Sample Size/ Design</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman RM, et al., 2000</td>
<td>n = 8 / randomized, controlled</td>
<td>MDD</td>
<td>0.5mg/kg I.V. ketamine y over 40 min</td>
<td>HDRS items related to SI</td>
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<tr>
<td>Price RB, et al., 2009</td>
<td>n = 26 / open study</td>
<td>TRD</td>
<td>0.5mg/kg I.V. ketamine hydrochloride over 40 min. 9 patients received thrice weekly ketamine infusions for 12 days.</td>
<td>MADRS-SI</td>
</tr>
<tr>
<td>DiazGranados N, et al., 2010</td>
<td>n = 33 / open study</td>
<td>MDD</td>
<td>0.5mg/kg I.V. ketamine hydrochloride over 40 min.</td>
<td>SSI, MADRS, HDRS, BDI</td>
</tr>
<tr>
<td>Larkin GL, Beautrais AL., 2011</td>
<td>n=14 / open study</td>
<td>SI patients in ER</td>
<td>0.2 mg./ kg IV ketamine (0.2 mg/kg) over 1–2 min.</td>
<td>MADRS</td>
</tr>
<tr>
<td>Zarate CA Jr, et al., 2012.</td>
<td>n = 15 / randomized, controlled</td>
<td>Bipolar 1 or 2 with current depressive episode</td>
<td>0.5mg/kg of ketamine hydrochloride intravenously over 40 min.</td>
<td>MADRS-SI, HDRS, BDI</td>
</tr>
<tr>
<td>Price RB, et al., 2014.</td>
<td>n = 57 / Double blind, randomized controlled</td>
<td>TRD</td>
<td>0.5 mg /kg I.V. ketamine midazolam (active placebo) = 0.045mg/kg over 40 min.</td>
<td>BSS, MADRS-SI, QIDS-SR, IAT.</td>
</tr>
<tr>
<td>Murrough J.W., et al., 2015</td>
<td>n = 24 / randomized, controlled</td>
<td>Depression and Anxiety spectrum with significant SI</td>
<td>0.5 mg/kg ketamine IV midazolam (active placebo) = 0.045mg/kg over 40 min in addition to standard of care.</td>
<td>BSI, MADRS-SI. (Other scales conducted: QIDS-SR, CHRT, CAST, BPRS, CADS, YMRS, PRISE, C-SSRS.)</td>
</tr>
<tr>
<td>Ballard, Elizabeth D., et al., 2015</td>
<td>n = 60 / randomized, crossover</td>
<td>MDD and BD</td>
<td>0.5mg/kg I.V. ketamine hydrochloride over 40 min or saline infusion as placebo.</td>
<td>HAM-D, MADRS, BDI items, and SSI</td>
</tr>
</tbody>
</table>
MADRS Suicidal Ideation Question

Mean MADRS suicide score vs. Time After Ketamine Infusion

Error Bars: +/- 1 SD
Ketamine treatment for suicidal ideation: a double edged sword

Clinically to provide greatly needed help to acutely suicidal patients

Experimentally to help tease out underlying mechanisms of suicide risk
Model Suicide Risk Progression—Factors Amenable to Rapid Change

- Depression
  - Alcohol
  - Physical/Sexual Abuse
  - Mania Psychosis

- Hopelessness
  - Female
  - White
  - Anxiety
  - Financial stressors
  - Unstable Housing
  - Physical Illness

- Suicidal Ideation
  - Male
  - Cocaine
  - Aggressive
  - Violent offense

- Impulsivity
  - No treatment

- Suicide Attempt
  - Traumatic Life Events
  - Lack of Coping Skills
  - Pain

- Completed Suicide
  - Access to Lethal Means
  - Male
  - Violent offense

- Completed Suicide
  - Lack of Social support
NIMH Research Domain Criteria (RDoC)

**Goal:** To understand psychiatric dysfunction by biological and behavioral underpinnings

**Five Domains:**
- Negative Valence
- Positive Valence
- Cognitive Systems
- Systems for Social Processes
- Arousal/Modulatory Systems
### Table 1. Effects of ketamine on measures of suicidal ideation, anxiety, and hopelessness

<table>
<thead>
<tr>
<th></th>
<th>60 minutes</th>
<th>120 minutes</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
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<tbody>
<tr>
<td></td>
<td>PL</td>
<td>KT</td>
<td>PL</td>
<td>KT</td>
<td>PL</td>
</tr>
<tr>
<td>Beck Scale for SI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean % of baseline</td>
<td>95.1*</td>
<td>26.6*</td>
<td>-</td>
<td>-</td>
<td>46.0</td>
</tr>
<tr>
<td>MADRS SI question</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean % of baseline</td>
<td>61.9</td>
<td>23.9</td>
<td>50.2*</td>
<td>7.14*</td>
<td>41.1*</td>
</tr>
<tr>
<td>Beck Anxiety Inventory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAI Percent of baseline</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>64.1</td>
</tr>
<tr>
<td>Beck Hopelessness Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of Baseline</td>
<td>95.1</td>
<td>73.4</td>
<td>87.9</td>
<td>65.1</td>
<td>69.3</td>
</tr>
</tbody>
</table>

**Abbreviations:** Placebo (PL), ketamine (KT), suicidal ideation (SI), Montgomery–Åsberg Depression Rating Scale (MADRS).

* P < 0.05.
NNDC Ketamine Biomarkers Study

A Single-Arm, Open-Label Biomarker Development Clinical Trial of Ketamine

for Non-Psychotic Unipolar Major Depression and Bipolar I or II Depression
Study Design

**A. Mandatory Acute Phase**
- Day 1
  - Ketamine 0.5 mg/kg IV
  - Up to Day 8

**Optional Continuation Phase**
- Week 1
  - Ketamine 0.5 mg/kg IV
  - (once weekly x 4 weeks)

**B. Study Overview**
- Blood sample, 20cc
- Saliva sample, 5cc
- 2 hr. post-infusion
- Infusion 1
  - Infusion 2
  - Infusion 3
  - 7 days after Infusion 1

**Figure 3.** The core clinical protocol consists of a mandatory acute phase and an optional continuation phase (Panel A). Up to 8 days are allowed including the first infusion day (Day 1) to administer 3 IV ketamine infusions (0.5 mg/kg, 100 minutes) during the acute phase. Acute phase remitters at specific sites may receive continuation phase infusions. Biological sample collection schedule is summarized in Panel B.
PROBLEMS IN PREVENTION OF SUICIDE:

Identification of those at risk

Provision of appropriate level of care in an appropriate time frame

Treatments that are specific, rapid and effective
Our Goal and our Challenge:

Clinically Meaningful Change

Clinically Meaningful Time Frame

Setting where Patients seek help
Thanks!
Thanks!

• Patients and Clinicians in PES

• Research Staff: Jadienne Lord, Yoav Domaney, MD
• Raisa Tikhtman, Arielle Tucker
  – Courtney Thornton, UAB

• Collaborators: Erik Nelson, Cal Adler, John Pestian,
  – Rick Shelton, Karen Cropsey: UAB
Glad to be a part of your family...