Panel
42. Army STARRS Suicide Research: From Bench to Battlefield

42.1 The Army STARRS Study Plan
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Background: For the US Army the rate of completed sucides increased substantially during the conflicts in Iraq and Afghanistan. Concern for Army soldiers as well as the national security brought the US Army and NIMH together to address this national issue. In fact suicide is a problem for the entire nation: The number of suicides in the United States far exceeds the number of homicides and approaches the number of fatalities from Motor Vehicle Collisions. The number of suicide attempts per year is about 1 million (in adults over age 18).
Methods: The Army Study to Assess Risk and Resilience in Servicemembers is a comprehensive Framingham like study to identify risk and resilience factors for suicide behaviors. The goal of Army STARRS is develop actionable findings to assist the Army in addressing suicide risk in soldiers. The study is funded at present for 5 years at $65 million dollars. The study includes 6 components: the Historical Data Study; New Soldier Study; All Army Study, Pre/Post Deployment Study; SHOS-A, and SHOS-B. Each component addresses different phases of suicide risk. Data collection includes assessments of risk and resilience factors, potential endophenotypes, blood collection (at joining the army and pre and post deployment) and available historical data. Overall the historical dat includes over 1.6 million soldiers and over i billion lines of data. The direct assessments will include nearly 100,000 soldiers in the various components of the study and nearly 40,000 soldiers providing blood samples.
Results: The components of the Study are addressing specific hypotheses on suicide risk with the goal of identifying concentrated risk to assist in direct health care and interventions. Genetic risk and resilience factors as well as gene x environment interactions are being identified.
Conclusions: The long-term value of the Army STARRS study is substantial. It provides the opportunity to move psychiatric care and the science of suicide behavior to both "risk calculation" in clinical care as in the Framingham studies and greatly advance the genetic determination of risk and resilience endophenotypes.
Disclosure: R. Ursano, Nothing to Disclose.

42.2 Executive Functioning and Suicidal Behavior among Soldiers: Results from the Army STARRS Study
Matthew Nock*

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Background: Suicide is the second leading cause of death among 25-34 year olds in the U.S. The rate of suicide among U.S. Army soldiers is even higher, following a marked increase in recent years. Given that people considering suicide may be unwilling or unable to report on their level of risk, a key challenge for suicide research is the identification of objective, behavioral or biological risk markers. Prior research suggests that deficits in executive functioning, such as problems with impulsiveness, cognitive flexibility, attention, and working memory may increase the risk of suicidal behavior (Keilp et al, 2001; Harkavy-Friedman et al, 2006). In an effort to test the potential utility of performance-based measures of executive functioning as behavioral risk markers for suicidal thoughts and behaviors, the current study examines: (a) the extent to which soldiers who have experienced suicide ideation and suicide attempts show deficits in executive functioning, and (b) the extent to which computer-based measures of executive functioning can improve the statistical prediction of recent suicidal behavior.
Methods: Data are from the New Soldier Study component of Army STARRS. In this study, new Army recruits ($N > 25{,}000$) complete a comprehensive, self-administered, computerized battery of eight neurocognitive tests that include measures of executive functioning, such as the: Go-No-Go test, continuous performance test, conditional exclusion test, and n-back test. Soldiers also complete a comprehensive, computer-administered survey that assesses history of suicidal behavior, mental disorders, and other putative risk and resilience factors. This presentation reports on the associations between executive functioning and suicidal thoughts and behaviors.
Results: Results reveal that: (a) these tests, modified in the current study for mass self-administration, show good psychometric properties, and (b) overall, poor performance on measures of executive functioning is associated with recent (past 30 days) suicide ideation and attempts ($rs = -.32$ to $-.04$), $R2 = .12$-$.19$, but not with lifetime suicide ideation and attempts ($rs = -.04$ to $.01$), $R2 = .01$-$.02$. This presentation also will include the results of tests of the incremental predictive validity of deficits in executive functioning.
Conclusions: Executive functioning deficits are associated with recent suicidal behavior among U.S. Army soldiers. The cross-sectional, bivariate nature of these analyses does not allow for any strong inferences about the association between executive functioning and suicidal behavior. Additional analyses, from this study and others, are needed to better understand the nature of this association. Nevertheless, these preliminary data support future efforts aimed at identifying behavioral markers for suicidal thoughts and behaviors.
Disclosure: M. Nock, Nothing to Disclose.

42.3 A Beating of Minds: Suicide and Traumatic Brain Injury
Murray B. Stein*

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Background: Suicide is a major problem for the US military. Studies suggest that suicidal thoughts, attempts, and completed suicides all increase in concert with deployments. As part of the Army STARRS goal of delineating risk and resiliency markers for suicide (and other deployment-related mental health problems), we examined associations between various putative risk factors – including self-reported history consistent with various levels of severity of traumatic brain injury (TBI) – and suicidality in a representative sample of over 3,000 Army personnel in the All-Army Survey (AAS). The AAS is designed to be a representative snapshot survey of all Army personnel exclusive of those in training.
Methods: The analysis of correlates reported here focuses on predictors of current, past 30-day, and past 12-month suicidality. The latter was broken down into: ideation, plan(s), attempt(s), and other forms of self-destructive behavior. We report conditional prevalence as well as odds-ratios (ORs) based on multiple logistic regression analyses.
Results: 13.5% of AAS respondents reported lifetime histories of suicidal ideation and 6.4% reported lifetime histories of self-destructive behaviors. 3.4% of AAS respondents reported lifetime histories of suicide plans (3.4%) and 2.9% reported lifetime histories of suicide attempts. in bivariate analyses, various levels of probable TBI were associated in a dose-response relationship (OR ranging from 1.7 to 4.0) with increased 12-month likelihood of suicide attempt(s) and/or self-destructive behaviors. At the extreme, the 7.1% of AAS respondents who experienced four or more types of head, neck, or blast injuries are 3.0-4.7 times as likely as those who experienced none to have 12-month suicidality.
Conclusions: One potentially important implication of these results that needs to be sorted out more exactly in future AAS analyses is that much of the recent suicidality associated with head, neck, or blast injuries among Army personnel appears to be associated with injuries that occurred prior to entering the Army, although perhaps exacerbated by subsequent repeat injuries that occurred while in the Army. If this is the case, it could have important intervention implications.

Disclosure: M. Stein, **Part 1:** Up To Date: Co-Editor-in-Chief for Psychiatry Content Depression and Anxiety (journal): Deputy Editor, **Part 2:** University of California San DiegoVA San Diego Healthcare System Up To Date Depression and Anxiety (journal): Wiley Press.

42.4 TBI and Medical Illness as Predictors of Suicide Risk in US Army Soldiers

Michael Schoenbaum*

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Background: The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS; www.armystarrs.org) is the largest study of mental health risk and resilience ever conducted among military personnel. The study has several major components, including a unique historical database of administrative data on the characteristics, experiences and exposures of the 1.6 million individuals who served on active duty in the US Army between 2004 and 2009. This includes soldiers with adverse outcomes, particularly suicide or other manners of death, as well as those with positive outcomes. We examine the association between traumatic brain injury and other types of medical illness and injury and subsequent risk of suicide, as part of a broader effort to identify predictors of risk and resilience in soldiers.
Methods: We conduct case-control analyses, using discrete time survival models, to estimate the association of indicators of traumatic brain injury and other types of medical illness and injury and subsequent risk of suicide. We focus particularly on "concentration of risk," i.e., the extent to which we can use data on TBI, other medical illness/injury, and other covariates to identify subgroups of soldiers with especially elevated suicide risk. Such empirical information would enable the Army to target suicide prevention/intervention efforts to high-risk groups.
Results: We report the independent associations between indicators of TBI and of other medical illness and injury, based on health care claims and encounter data from the military health system, on subsequent risk for suicide death. We also report the extent to which these predictors, along other other measures of soldiers' characteristics and experiences, support the development of predictive algorithms for suicide risk.
Conclusions: Predictive risk algorithms based on medical and other Army and Department of Defense administrative data can be used to identify subgroups of soldiers with particularly elevated suicide risk. These findings may help the Army to focus prevention/intervention programs, and may suggest hypotheses to be tested in future research using primary survey, neurocognitive and biological data.
Disclosure: M. Schoenbaum, Nothing to Disclose.

Thursday, December 06, 2012

Mini Panel
43. Beyond Ketamine, Can Selective Targeting of the NMDA Receptor Produce Antidepressant Response without Psychotomimetic Effects: Clinical Results with Three Novel Compounds

43.1 Beyond Ketamine: Next generation NMDA Antagonists Show Rapid Antidepressant Effects, without Psychotomimetic Effects

Nancy Diazgranados*

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Background: The rapid onset of antidepressant effects with ketamine has led to exploring compounds that also modulate the N-methyl-D-aspartate (NMDA) receptor complex with the hope of developing drugs with rapid antidepressant effects, but without ketamine's adverse properties. Two studies were conducted in treatment-resistant major depressive disorder (TRD) determine whether they produced rapid antidepressant effects: study 1 was with a low-trapping NMDA channel blocker (AZD6765) and study 2 was with a selective NR2B antagonist (MK-0657).
Methods: Two randomized, crossover, placebo-controlled studies were conducted in treatment-resistant major depressive disorder (TRD) at NIMH. In study 1, after a two week drug-free period, 22 subjects received an intravenous infusion of either AZD6765 (150 mg) or placebo on two test days one week apart. The MADRS and HAM-D were used to rate subjects at baseline, at 60, 80, 110, and 230 minutes post-infusion, and on Days 1, 2, 3, and 7 post-infusion. In study 2, TRD subjects underwent a one-week drug-free period and were subsequently randomized to receive either MK-0657 monotherapy (4-8 mg/day) or placebo for 12 days.
Results: Study 1: Depressive symptoms as measured by MADRS, significantly improved in subjects receiving AZD6765 compared to placebo (effect size $d = 0.40$); the greatest improvement over placebo was at 80 and 110 minutes. On the HAM-D scale, the drug difference was significant ($d = 0.49$) with the largest differences at the same time points in addition to day 2. Thirty-two percent of subjects responded to AZD6765 and 15% to placebo at some point during the trial. There were no differences in psychotomimetic or dissociative symptoms at anytime between groups. AZD6765 was well-tolerated. In study 2, significant antidepressant effects were observed as early as Day 5 in patients receiving MK-0657 compared to placebo as assessed by the HAM-D and Beck Depression Inventory; however, no improvement was noted when symptoms were assessed with the MADRS, the primary efficacy measure. No serious or dissociative adverse effects were observed in patients receiving this oral formulation of MK-0657.
Conclusions: In patients with treatment-resistant major depressive disorder, rapid but short-lived antidepressant effects resulted from a single intravenous dose of a low trapping NMDA channel blocker. An oral selective NR2B antagonist showed onset of antidepressant effects by day 5. Both compounds at the dose tested, were not associated with psychotomimetic or dissociative side effects or significant blood pressure changes. This suggests that the acute antidepressant response of drugs that target the NMDA receptor complex is not dependant or necessarily associated with psychotomimetic effects. Furthermore, the potential of un-blinding of the studies due to medication side effects that has been questioned with the ketamine studies was not present with this two compounds.
Disclosure: N. Diazgranados, Nothing to Disclose.

43.2 A Phase 2, Randomized, Double Blind, Single Intravenous Dose Study of GLYX-13, an NMDA Receptor Glycine Site Functional Partial Agonist, in Subjects with Major Depressive Disorder with Inadequate Response to Antidepressant Medication

Ronald M. Burch*

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Background: Previous studies of the NMDA receptor antagonists ketamine and CP-100,606 have demonstrated rapid and robust antidepressant effects following single IV administration. Both of these agents, like other NMDA receptor antagonists, are also associated with acute psychotomimetic effects. Unlike full antagonists, glycine site partial agonists such as D-cycloserine, have not been associated with acute psychotomimetic effects. GLYX-13 is a glycine site functional partial agonist at the NMDA receptor. In animals it does not cause any behavioral effects referable to psychotomimetic effects at doses 100 times greater than doses that elicit pharmacologic effects in antidepressant models such as Porsolt assay.
Methods: Subjects who had $<25\%$ reduction in depressive symptoms during the current episode assessed using the Antidepressant Treatment Response Questionnaire (ATRQ) were admitted to the clinic prior to dosing and remained in the clinic until the 24 h evaluations were completed. Hamilton Depression