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14. ABSTRACT The study is designed to evaluate the utility of levels of two phospholipids in serum as a marker of past drinking behavior across month-level time horizons, in an attempt to improve ability to measure alcohol quantity consumed and associated damage better than can be done with ethyl alcohol level measures and other existing tests that only measure very recent exposure and poorly reflect quantity consumed. This will be achieved by correlating detailed questionnaire data on alcohol consumption with serum phospholipid levels in subjects not selected for alcohol abuse (part I) and subjects under alcohol abuse treatment (part II). The Department of Defense-funded study will conduct Part I at the VA hospital and Part II at the Fairbanks treatment facility. Part I involves a single study session (n=280), while Part II will involve serial blood draws and phospholipid measures at several treatment visits (n=60). The study is open to 280 subjects for Part I, and 60 subjects for part II. Part I has 179 consented, and 18 screen fails; Part II has 33 consented (one withdrew from the study) and 8 screen fails. The study is currently active and analysis has not been completed. Since the inception of the study, we have not experienced any problems with subjects' recruitment. To date, we have recruited 197 subjects into Part I of the study and 41 subjects into part II.					
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INTRODUCTION

The abuse of alcohol is a major public health problem, and the diagnosis and care of patients with alcohol abuse and dependence is hampered by the lack of tests that can detect dangerous levels of drinking or relapse during therapy. Such tests would be valuable to screen for excessive alcohol use, to monitor subjects during alcohol rehabilitation, and to monitor abstinence in subjects with alcohol-induced organ injury (such as those with alcoholic liver disease). Alcohol itself is present in blood or urine samples for only a short time after stopping drinking, and thus doesn't provide information beyond the most recent period of alcohol use. At present, we routinely check for AST/ALT, Mean Corpuscular volume (MCV), and carbohydrate deficient transferrin (CDT) for ongoing alcohol use. However, these tests do not bear a relationship to quantity of alcohol consumed, and do not become abnormal quickly when patients relapse into drinking. The goal of this study is to determine if the levels of serum phospholipids (sphingomyelin and lysophosphatidylcholine) correlate with excessive alcohol use as defined by the NIH/NIAAA. The long term goal of our proposal is to determine the diagnostic utility of phospholipids, sphingomyelin and lysophosphatidylcholine, as the potential biomarkers for excessive alcohol use (EAU).

BODY

The proposed project responds directly to the Fiscal Year 2011, Peer Reviewed Medical Research Program (PRMRP) announced by the Department of Defense; which calls for scientific research in the area of drug and alcohol use. Our proposal is to determine the diagnostic utility of phospholipids, sphingomyelin and lysophosphatidylcholine, as the potential biomarkers for excessive alcohol use (EAU). Drinking becomes excessive when it causes or elevates the risk for alcohol-related problems or complicates the management of other health problems. According to the NIH/NIAAA (**National Institute on Alcohol Abuse and Alcoholism**), excessive drinking is defined as men who drink more than 4 standard drinks in a day (or more than 14 per week) and women who drink more than 3 drinks in a day (or more than 7 per week) (1). Non-civilian military personnel have been deployed in support of the war efforts in Afghanistan (Operation Enduring Freedom, OEF) and Iraq (Operation Iraqi Freedom, OIF) since September 11, 2001. These sustained combat operations have resulted in military personnel experiencing physical threat or actual injury during the deployment and difficult adjustments during post-deployment period (2). Negative life stress is a major contributor to the onset and exacerbation of EAU; a rising epidemic reported to be as high as 40% among returning veterans (3). The prevalence of EAU is alarming, and the vigilance and action to identify veterans with EAU is of importance. The consequences of under-detection of EAU, thus delayed intervention are serious because relative risk of alcohol-related health conditions such as alcoholic hepatitis, alcoholic cirrhosis, pancreatitis, and hepatocellular carcinoma, is increased with the amounts and duration of alcohol consumed per day (4).

Why is identifying the potential biomarkers with improved sensitivity and specificity to screen for EAU important? While detailed efforts have been made to construct interview formats that correctly quantify alcohol intake, such as Alcohol Use Disorder Identification Test Consumption (AUDIT-C)(5), CAGE (6), or including reports from collateral individuals (family and friends who interact with the subject)(7), these approaches have their limitations. This is especially true in cases where individuals are motivated to deny or minimize the magnitude of drinking behavior to mitigate personal ramifications

(8). Self-reporting mechanisms will continue to have utility in clinical and research settings; however, their use is constrained by limitations in time, resources, and training of personnel when using self report mechanisms. One study showed that most primary care physicians do not screen for alcohol problems with questionnaires during clinic visit (9). However, they often conduct a battery of clinical tests such as gamma-glutamyltransferase (GGT), mean corpuscular volume (MCV), and aspartate aminotransferase (AST). Elevation of these markers could alert physicians to possible excessive drinking, though, these tests are neither sensitive nor specific for EAU (9;10). These limitations are the basis of this proposal to identify reliable potential markers of EAU, based on our preliminary data in section C (Figures 3-5). The addition of sensitive biomarkers not only would confirm the self-report but would provide results from an objective biochemical test to help physicians to motivate patients to either stop drinking or cut back to low-risk levels.

Besides questionnaires, several laboratory tests have been used to screen for alcohol use in clinical practice. Among them are GGT, MCV, AST, alanine aminotransferase (ALT) sialylation of apolipoprotein J, carbohydrate deficient transferrin (CDT), 5-hydroxytryptophan and ethyl glucuronide (11). However, we found that the ability of these markers to determine the levels of alcohol drinking revealed low sensitivities and specificities (10). It is possible that many of these commonly used markers are related to hepatic function; which is well known to be altered with EAU. Hepatic function is also impaired; however, in several conditions; which lead to false positives and reduced specificities (11). Moreover, these tests do not bear a linear relationship to the quantity of alcohol consumed, and do not become abnormal quickly when treated patients relapse into drinking (12). Taken together, new markers with good sensitivity, specificity, and ease of use are needed to screen for EAU and for monitoring of abstinence.

Metabolomics, the study of metabolites (*including lipid molecules*) is an emerging and potentially important area of basic and translational research. Altered metabolite levels (e.g. cholesterol is a marker for cardiovascular diseases and blood sugar level is a marker for diabetes) have been shown to be the hallmark of many metabolic diseases. Certain lysophospholipids have recently been recognized as important cell signaling molecules (13), and concentrations of these lipids are tightly controlled in biological systems and thus their levels may be markers of diseases. *The idea of using a lipidomic approach as a screening tool for EAU is novel and our preliminary data showed promising results that certain lipids especially sphingomyelin (SM) and lysophosphatidylcholine (LPC) might improve the sensitivity and specificity to screen for EAU.* Mechanistically, several lines of evidence suggest that alteration in serum phospholipids occurs with EAU. Alcohol activates acidic sphingomyelinase, an important enzymes involved in sphingolipid metabolism (14) and it induces fatty acid synthesis pathways which is regulated by sphingomyelinase, another form of phospholipid (15). In accordance with our study in mice fed with ethanol for 4 weeks (16), we found significant changes in the levels of serum phospholipids (especially SM and LPC) in human subjects with documented EAU, and observed the reversal trend in their levels after abstinence, suggesting that these markers, either used alone or in combination with currently available laboratory tests, might be effective to screen for EAU. We will systematically study this in detail this proposal.

KEY RESEARCH ACCOMPLISHMENTS

The study is designed to evaluate the utility levels of two phospholipids in serum as a marker of past drinking behavior across month-level time horizons, in an attempt to improve ability to

measure alcohol quantity consumed and associated damage better than can be done with ethyl alcohol level measures and other existing tests that only measure very recent exposure and poorly reflect quantity consumed. This will be achieved by correlating detailed questionnaire data on alcohol consumption with serum phospholipid levels in subjects not selected for alcohol abuse (part I) and subjects under alcohol abuse treatment (part II). The Department of Defense-funded study will conduct Part I at the VA hospital and Part II at the Fairbanks treatment facility. Part I involves a single study session (n=280), while Part II will involve serial blood draws and phospholipid measures at several treatment visits (n=60). The study is open to 280 subjects for Part I, and 60 subjects for part II. Part I has 179 consented, and 18 screen fails; Part II has 33 consented (one withdrew from the study) and 8 screen fails. The study is currently active and analysis has not been completed. Since the inception of the study, we have not experienced any problems with subjects' recruitment. To date, we have recruited 197 subjects into Part I of the study and 41 subjects into part II.

REPORTABLE OUTCOMES

There are no reportable outcomes.

CONCLUSION

Due to continuous recruitment, no analysis have been performed.

REFERENCES

- Agresti, A. & Finlay, B. (1997). *Statistical Methods for the Social Sciences*. (3rd ed.) Upper Saddle River, NJ: Prentice-Hall, Inc.
- Allen, J. P., Litten, R. Z., Fertig, J. B., & Sillanaukee, P. (2000). Carbohydrate-deficient transferrin, gamma-glutamyltransferase, and macrocytic volume as biomarkers of alcohol problems in women. *Alcohol Clin Exp Res*, 24(4), 492-496.
- Allison, P. D. (2002). *Missing Data*. Thousand Oaks, CA; London: Sage Publications.
- Ames, G. M., Cunradi, C. B., Moore, R. S., & Stern, P. (2007). Military culture and drinking behavior among U.S. Navy careerists. *Journal Of Studies On Alcohol And Drugs*, 68(3), 336-344.
- Back, S. E., Jackson, J. L., Sonne, S., & Brady, K. T. (2005). Alcohol dependence and posttraumatic stress disorder: differences in clinical presentation and response to cognitive-behavioral therapy by order of onset. *Journal of Substance Abuse Treatment*, 29(1), 29-37.
- Box-Steffensmeier, J. M. & JONES, B. S. (2004). *Timing and Political Change: Event History Modeling in Political Science*. Ann Arbor, MI: University of Michigan Press.
- Bozarth, M. A. (1987). Neuroanatomical boundaries of the reward-relevant opiate-receptor field

in the ventral tegmental area as mapped by the conditioned place preference method in rats. *Brain Res*, 414(1), 77-84.

- Bray, R., Hourani, L. L., Rae Olmsted, K. L., Witt, M., Brown, J. M., Pemberton, M.R. et al. (2006). 2005 Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel: A Component of the Defense Lifestyle Assessment Program (DLAP) [prepared for the Assistant Secretary of Defense, U.S. Department of Defense]. *Cooperative Agreement No.DAMD 17-00-2-0057/RTI/7841/106-FR*.
- Calhoun, P. S., Elter, J.R., Jones, E.R., Kudler, H., & Straits-Troster, K. (2008). Hazardous alcohol use and receipt of risk-reduction counseling among U.S. veterans of the wars in Iraq and Afghanistan. *J.Clin.Psychiatry*, 69(11), 1686-1693.
- Calsyn, R.J., Klinkenberg, W.D., Morse, G.A., Miller, J., & Cruthis, R. (2004). Recruitment, engagement, and retention of people living with HIV and co-occurring mental health and substance use disorders. *AIDS Care*, 16, S56-S70.
- Carol, B. C. (2007). Drinking Level, Neighborhood Social Disorder, and Mutual Intimate Partner Violence. *Alcoholism: Clinical and Experimental Research*, 31(6), 1012-1019.
- Chuang, Y. C., Ennett, S.T., Bauman, K.E., & Foshee, V. A. (2005). Neighborhood Influences on Adolescent Cigarette and Alcohol Use: Mediating Effects through Parent and Peer Behaviors. *Journal of Health and Social Behavior*, 46(2), 187-204.
- Cook, J.A. & Wright, E.R. (1995). Medical sociology and the study of severe mental illness: reflections on past accomplishments and directions fo future research. *Journal of Health and Social Behavior*, 36(Extra Issue), 95-114.
- Cottler, L. B., Compton, W.M., Ben-Abdallah, A., Horne, M., & Claverie, D. (1996). Achieving a 96.6 percent follow-up rate in a longitudinal study of drug abusers. *Drug & Alcohol Dependence*, 41(3), 209-217.
- Cuadrado, A., Fabrega, E., Casafont, F., & Pons-Romero, F. (2005). Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl.*, 11(4), 420-426.
- D'Mello, T., Williams, E., Eaton, C. M., & Pflantz, C.S. (2007). Stressors Prior to and Methods of Suicide, U.S. Air Force, 2000-2005. *Medical Surveillance Monthly Report, MSMR*, 13(2), 8-9.
- Dennis, M.L., Titus, J.C., White, M.K., Unsicker, J. I., & Hodgkins, D. (2002). *Global Appraisal of Individual Needs (GAIN): Administration guide for the GAIN and related measures*. Bloomington, IL: Chestnut Health Systems.
- Dinubile, M. J. (2007). Plasma gelsolin: in search of its raison d'etre. Focus on "Modifications of cellular

responses to lysophosphatidic acid and platelet-activating factor by plasma gelsolin". *Am J Physiol Cell Physiol*, 292(4), C1240-C1242.

Eggleston, A. M., Straits-Troster, K., & Kudler, H. (2009). Substance use treatment needs among recent veterans. *North Carolina Medical Journal*, 70(1), 54-58.

Encandela, J. A., Korr, W. S., Hulton, K., Koeske, G. F., Klinkenberg, W.D., Otto-Salaj, L.L. et al. (2003). Mental health case management as a locus for HIV prevention: Results from case-manager focus groups. *Journal of Behavioral Health Services & Research*, 30(4), 418-432.

Ewing, J. A. (1984). Detecting alcoholism. The CAGE questionnaire. *JAMA*, 252(14), 1905-1907.

Ferrier-Auerbach, A.G., Kehle, S. M., Erbes, C.R., Arbisi, P.A., Thuras, P., & Polusny, M.A. (2009). Predictors of alcohol use prior to deployment in National Guard Soldiers. *Addictive Behaviors*, 34(8), 625-631.

Gibbons, R. D., Hedeker, D., Elkin, I., Waternaux, C., Kraemer, H.C., Greenhouse, J.B. et al. (1993). Some conceptual and statistical issues in the analysis of longitudinal psychiatric data. *Archives of General Psychiatry*, 50, 739-750.

Ginzburg, H.M. (2009). Meeting the Emotional Needs of Returning War Zone Veterans. *Psychiatric Annals*, 39(2), 37-44.

Golka, K., Sondermann, R., Reich, S. E., & Wiese, A. (2004). Carbohydrate-deficient transferrin (CDT) as a biomarker in persons suspected of alcohol abuse. *Toxicol Lett*, 151(1), 235-241.

Graham, D. P., Cardon, A. L., & Uhl, G. R. (2008). An update on substance use and treatment following traumatic brain injury. In *Addiction reviews 2008*. (pp. 148-162). Malden: Blackwell Publishing.

Hasin, D., Hatzenbuehler, M. L., Keyes, K., & Ogburn, E. (2006). Substance use disorders: Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and International Classification of Diseases, tenth edition (ICD-10). *Addiction*, 101 Suppl 1, 59-75.

Helander, A. (2003). Biological markers in alcoholism. *J Neural Transm Suppl*, (66), 15-32.

Hirsch, K. A. (2009). *sexual dysfunction in male operation enduring freedom/operation iraqi freedom patients with severe post-traumatic stress disorder*.

Hoge, C. W., Terhakopian, A., Castro, C. A., Messer, S. C., & Engel, C. C. (2007). Association of Posttraumatic Stress Disorder With Somatic Symptoms, Health Care Visits, and Absenteeism Among Iraq War Veterans. *Am J Psychiatry*, 164(1), 150-153.

- Huba, G. J., Melchior, L. A., Greenberg, B., Trevithick, L., Feudo, R., Tierney, S. et al. (2000). Predicting substance abuse among youth with, or at high risk for, HIV. *Psychology of Addictive Behaviors*, 14(2), 197-205.
- Hunt, J. R. & White, E. (1998). Retaining and tracking cohort study members. *Epidemiological Review*, 20(1), 57-70.
- Hussain, T. & Lokhandwala, M. F. (1997). Dopamine-1 receptor G-protein coupling and the involvement of phospholipase A2 in dopamine-1 receptor mediated cellular signaling mechanisms in the proximal tubules of SHR. *Clin Exp Hypertens.*, 19(1-2), 131-140.
- Indiana, N. G. (2009). *Indiana national guard government report as of october 21, 2009: total contributions to gwot* Indianapolis: JFHQ Public Affairs.
- Jacobson, I. G., Ryan, M.A.K., Hooper, T.I., Smith, T.C., Amoroso, P.J., Boyko, E. J. et al. (2008). Alcohol use and alcohol-related problems before and after military combat deployment. *JAMA: The Journal Of The American Medical Association*, 300(6), 663-675.
- Kennedy, P. (1985). *A Guide to Econometrics, Second Edition*. Cambridge, MA: MIT Press.
- King, L.A., King, D. W., Bolton, E. E., Knight, J. A., & Vogt, D. S. (2008). Risk factors for mental, physical, and functional health in Gulf War veterans. *J Rehabil.Res Dev*, 45(3), 395-407.
- Klinkenberg, W. D. & Calsyn, R. J. (1997). The moderating effects of race of return visits to the psychiatric emergency room. *Psychiatric Services*, 48(7), 942-945.
- Kooreman, H. E., Wright, E. R., McGrew, J. H., & Pescosolido, B. A. (1996). *central state hospital discharge study tracking report--december 1996* Bloomington, IN: Indiana Consortium for Mental Health Services Research.
- Kreft, I. G. (1994). Multilevel models for hierarchically nested data: potential applications in substance abuse prevention research. *NIDA Res Monogr*, 142, 140-183.
- Kreft, I.G.G. (1996). Are Multilevel Techniques Necessary? An Overview, Including Simulation Studies. [On-line].
- Kreft, I. G. G., DE LEEUW, J., & AIKEN, L. S. (1995). The effect of different forms of centering in hierarchical linear models. *Multivariate Behavioral Research*, 30(1), 1-21.
- Kroke, A., Klipstein- Grobusch, K., Hoffmann, K., Terbeck, I., Boeing, H., & Helander, A. (2001). Comparison of self-reported alcohol intake with the urinary excretion of 5-hydroxytryptophol:5-hydroxyindole-3-acetic acid, a biomarker of recent alcohol intake. *Br J Nutr*, 85(5), 621-627.

- Le-Niculescu, H., McFarland, M.J., Ogden, C.A., Balaraman, Y., Patel, S., Tan, J. et al. (2008). Phenomic, convergent functional genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism. *Am J Med Genet B Neuropsychiatr Genet*, 147B(2), 134-166.
- Liangpunsakul, S., Qi, R., Crabb, D. W., & Witzmann, F.A. (2010). Relationship between alcohol drinking and AST:ASLT ratio, MCV, GGT, apolipoprotein A1 and B in the United States population. *J Stud Alcohol* (in press)
- Marmar, C. R. (2009). *Mental health impact of afghanistan and iraq deployment: meeting the challenge of a new generation of veterans*.
- McAllister, D. J. & De Siervo, A. J. (1975). Identification of bisphosphatidic acid and its plasmalogen analogues in the phospholipids of a marine bacterium. *J Bacteriol.*, 123(1), 302-307.
- Menard, S. (1991). *Longitudinal Research*. Newbury Park, CA: Sage.
- Milliken, C. S., Auchterlonie, J. L., & Hoge, C. W. (2007). Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. *JAMA*, 298(18), 2141-2148.
- Mirola, W., Wright, E. R., McGrew, J. H., Pescosolido, B. A., & Miller, J. B. (1995). *Central state hospital discharge study tracking report--march 1995* Bloomington, IN: Indiana Consortium for Mental Health Services Research.
- Nissinen, A. E., Makela, S. M., Vuoristo, J. T., Liisanantti, M. K., Hannuksela, M. L., Horkko, S. et al. (2008). Immunological detection of in vitro formed phosphatidylethanol--an alcohol biomarker--with monoclonal antibodies. *Alcohol Clin Exp Res*, 32(6), 921-928.
- Openshaw, S. (1984). *The Modifiable Area Unit Problem: Concepts and Techniques in Modern Geography*. (vols. 38) Norwich, UK: GeoBooks.
- Pepe, M. S. (2000). An interpretation for the ROC curve and inference using GLM procedures. *Biometrics*, 56(2), 352-359.
- Perl, L. (2009). Veterans and Homelessness. *Congressional Research Service Report for Congress*, 7-5700(RL34024).
- Perry, B. L. & Wright, E. R. (2000). Social Integration and Patterns of Sexual Abuse among Gay, Lesbian, and Bisexual Youth.
- Pescosolido, B. A., Gardner, C. B., & Lubell, K. M. (1998). How people get into mental health services: Stories of choice, coercion, and 'muddling through' from 'first-timers'. *Social Science & Medicine*, 46(2), 275-286.

- Pescosolido, B. A., Wright, E. R., Alegria, M., & Vera, M. (1998). Social networks and patterns of use among the poor with mental health problems in Puerto Rico. *Medical Care*, 36(7), 1057-1072.
- Pescosolido, B. A., Wright, E. R., & Lutfey, K. (1999). The changing hopes, worries, and community supports of individuals moving from a closing long term care facility to community-based care. *Journal of Behavioral Health Services and Research*, 26(3), 276-288.
- Pescosolido, B. A., Wright, E. R., & Sullivan, W. P. (1995). Communities of care: A theoretical perspective on case management models in mental health. *Advances in Medical Sociology*, 6, 37-79.
- Petrucelli, B. (2007). Hospitalization Experience within One Year after Returning from Afghanistan or Iraq, January 2002-September 2006. *Medical Surveillance Monthly Report, MSMR*, 14(2), 2-10.
- Pietrzak, R. H., Johnson, D. C., Goldstein, M. B., Malley, J. C., & Southwick, S. M. (2009). Psychological resilience and postdeployment social support protect against traumatic stress and depressive symptoms in soldiers returning from Operations Enduring Freedom and Iraqi Freedom. *Depression and anxiety*, 26(8), 745-751.
- Raudenbush, S. W. & Bryk, A. S. (2002). *Hierarchical Linear Models: Applications and Data Analysis Methods*. (2nd ed.) Thousand Oaks, CA: Sage Publications, Inc.
- Resnik, L. J. & Allen, S. M. (2007). Using International Classification of Functioning, Disability and Health to understand challenges in community reintegration of injured veterans. *Journal of Rehabilitation Research & Development*, 44(7), 991-1005.
- Ross, B. M., Moszczynska, A., Peretti, F. J., Adams, V., Schmunk, G.A., Kalasinsky, K. S. et al. (2002). Decreased activity of brain phospholipid metabolic enzymes in human users of cocaine and methamphetamine. *Drug & Alcohol Dependence*, 67(1), 73-79.
- Samuelson, K. W., Neylan, T. C., Metzler, T. J., Lenoci, M., Rothlind, J., Henn-Haase, C. et al. (2006). Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. *Neuropsychology*, 20(6), 716-726.
- Shojania KG, Jennings A, Mayhew A. The effects of on-screen, point of care computer reminders on processes and outcomes of care. [Cochrane Database Syst Rev](#). 2009 Jul 8;(3):CD001096.
- Singer, J. D. & Willett, J. B. (2003). *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. New York, NY: Oxford University Press.
- Sofair, A. N., Barry, V., Manos, M. M., Thomas, A., Zaman, A., Terrault, N. A. et al. (2009). The Epidemiology and Clinical Characteristics of Patients With Newly Diagnosed Alcohol-related Liver Disease: Results From Population-based Surveillance. *J Clin Gastroenterol*.

- South, B. T. (2008). Indiana leads nation in Army Guard, Reserve deployments. 24/7 News Report [On-line]. Available: <http://www.southbendtribune.com/apps/pbcs.dll/article?AID=/20080107/News01/390871545/1052/News01>
- Stephanson, N., Helander, A., & Beck, O. (2007). Alcohol biomarker analysis: simultaneous determination of 5-hydroxytryptophol glucuronide and 5-hydroxyindoleacetic acid by direct injection of urine using ultra-performance liquid chromatography-tandem mass spectrometry. *J Mass Spectrom*, 42(7), 940-949.
- Street, A.E., Vogt, D., & Dutra, L. (2009). A new generation of women veterans: Stressors faced by women deployed to Iraq and Afghanistan. *Clinical Psychology Review, In Press, Corrected Proof*.
- Sutphen, R., Xu, Y., Wilbanks, G. D., Fiorica, J., Grendys, E. C., JR., LaPolla, J. P. et al. (2004). Lysophospholipids are potential biomarkers of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*, 13(7), 1185-1191.
- Taylor, J. E., Haddock, K., Poston, W. S. C., & Talcott, W. G. (2007). Relationship between patterns of alcohol use and negative alcohol-related outcomes among U.S. Air Force recruits. *Military Medicine*, 172(4), 379-382.
- Tourangeau, R. & Smith, T. W. (1996). Asking Sensitive Questions: The Impact of Data Collection Mode, Question Format, and Question Context. *Public Opinion Quarterly*, 60, 275-304.
- Verdejo-Garcia, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2007). Negative emotion-driven impulsivity predicts substance dependence problems. *Drug and Alcohol Dependence*, 91, 213-219.
- Wasserman, S. & Faust, K. B. (1994). *Social Network Analysis: Methods and Applications*. New York, NY: Cambridge University Press.
- White, T. & Wright, E. R. (1996). *Interviewing in the mental health arena: the icmhsr handbook*. Bloomington, IN: Indiana Consortium for Mental Health Services Research.
- Williams, M. L., Freeman, R. C., Bowen, A.M., Zhao, Z., Elwood, W.N., Gordon, C. et al. (2000). A Comparison of the Reliability of Self-Reported Drug Use and Sexual Behaviors Using Computer-Assisted Versus Face-to-Face Interviewing. *AIDS Education and Prevention*, 13(3), 199-213.
- Wise, R.A. & Bozarth, M. A. (1985). Brain mechanisms of drug reward and euphoria. *Psychiatr Med*, 3(4), 445-460.
- Wright, E. R. (1995). Personal Networks and Anomie: Exploring the Sources and Significance of Gender Composition. *Sociological Focus*, 28(3), 261-282.

- Wright, E. R. (1999). HIV risk of mental illness clients across service sites. Ref Type: Unpublished Work
- Wright, E. R., GAYMAN, M. D., VIGGIANO, T., RAU, N. L., & LINDE, B. (2000). *caring for psychiatric patients in the general hospital emergency room: study report* Indianapolis, IN: Indiana Consortium for Mental Health Services Research.
- Wright, E. R., Gonzalez, C., Werner, J.N., Laughner, S.T., & Wallace, M. (1998). The Indiana Youth Access Project (IYAP): A model for responding to the HIV risk behaviors of gay, lesbian, and bisexual youth in the Heartland. *Journal of Adolescent Health*, 23(Suppl), 83-95.
- Wright, E. R., Miller, J. B., Pescosolido, B. A., & McDonel, E. C. (1994). *central state hospital discharge study tracking report--january 1994* Bloomington, IN: Indiana Consortium for Mental Health Services Research.
- Wright, E. R. & Myers, J. (1996). Peer-Based HIV Risk Reduction: A Network Approach to Assessing the Nature and Dynamics of Peer Influence.
- Wright, J. D., Allen, T. L., & Devine, J. A. (1995). Tracking non-traditional populations in longitudinal studies. *Evaluation and Program Planning*, 18(3), 267-277.
- WSBT.COM (2008). Indiana leads nation in Army Guard, Reserve deployments. 24/7 News Report [On-line]. Available: <http://www.wsbt.com/news/local/13496397.html>
- Xu, Y., Wang, D., & Wang, Z. (2009). Lipid generation and signaling in ovarian cancer. *Cancer Treat.Res*, 149, 241-267.
- Yamaguchi, K. (1991). *Event History Analysis*. Newbury Park, CA: Sage Publications, Inc.
- Zakhari, S. & Li, T.K. (2007). Determinants of alcohol use and abuse: Impact of quantity and frequency patterns on liver disease. *Hepatology*, 46(6), 2032-2039.
- Zhao, Z. & Xu, Y. (2009). An extremely simple method for extraction of lysophospholipids and phospholipids from blood samples. *J Lipid Res*.

APPENDICES

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