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Capacity building and collaborative research on cross-national studies in the Asian region

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ABSTRACT

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To build capacity and collaborative research for future cross-national studies in the Asian and Pacific Islander (API) region, priority research topics were identified and discussed at the April 2013 Conference to Promote Global Health in Taipei. These topics included: (1) neuroscience on human immunodeficiency virus (HIV)/hepatitis C virus (HCV) and amphetamine-type stimulants (ATS), led by Drs Linda Chang, Gene-Jack Wang, and Betty Tai; (2) ATS and mental health disorders, led by Drs Richard Rawson and Wilson Compton; and (3) HIV/HCV transmission and social networks, led by Drs Steven Shoptaw and Jacques Normand. Potential genetic studies spanning these topical areas as well as the importance of smoking cessation were further discussed, led by Dr Ming Li. Additional priority research topics were also identified: (4) drug use prevention; and (5) family involvement to improve treatment adherence and recovery. Workgroups on these topics will be formed to prioritize research questions within the respective topical area and to determine the next steps. The ultimate goal of these workgroups is to stimulate collaboration that will eventually lead to research studies addressing critical issues related to the rising substance abuse and HIV infection rates in many Asian countries and, at the same time, to advance the scientific knowledge of substance abuse and HIV infection.

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1. Background and introduction

The long-term goal of the Conference Series to Promote Global Health is to build capacity and facilitate collaboration among participating Asian countries and investigators to develop and conduct research addressing critical substance abuse and human immunodeficiency virus (HIV) issues in the Asian region. During the conference, Dr Wilson Compton [Director of the Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse (NIDA)] and Dr Jacques Normand (Director of AIDS Research Program, NIDA) both presented comprehensive information on NIDA funding resources and opportunities for training and research, particularly for international investigators and studies. Additionally, a suggestion was made to form workgroups on priority topics on which investigators from the United States and Asian countries can work together to formulate research questions, design studies, and carry out investigations.

Currently, Asian/Pacific Islander (API) countries have some of the highest rates of opiate, methamphetamine, alcohol, and tobacco use, as well as the highest rates of HIV transmission via injection drug use. Substance abuse is not only having crippling effects on the economies, family structures, criminal justice systems, and environment in API countries, but it also increases the prevalence of many comorbid illnesses, particularly HIV and hepatitis C virus (HCV). In most countries around the world, the prevalence of HIV infection is at least 22 times higher amongst those who inject drugs than the general population [1]. It is estimated that as many as 5 million drug users in Asia are living with HIV/AIDS, with injection drug use serving as the primary mode of transmission. HIV/HCV co-infection rates are rampant among injection drug users (IDUs) in many parts of Asia. These health risks are exacerbated by a lack of state-of-the-art interventions, inadequate access to treatment, the criminalization of drug use, and stigma associated with both substance use and HIV/AIDS, combined with limited infrastructure and expertise for addressing these issues on a local, community, and national level [1].

The tremendous multidisciplinary and world-class expertise and knowledge among the conference presenters and participants represent a great resource for international collaborations and scientific development in Asia. Collaborative efforts to develop and conduct cross-national studies in Asia to address Asia-specific problems in substance abuse and HIV are likely to offer tremendous opportunities and potential for scientific advancements and benefits to patient care. As an initial step in forming workgroups, efforts were devoted to identifying research priorities. Three topics were identified and discussed in the conference: (1) neuroscience on HIV, HCV, and amphetamine-type stimulants (ATS); (2) ATS and mental disorders; and (3) HIV/HCV transmission and social networks. Additional topics that were further identified include genetics of substance abuse, tobacco cessation, drug use prevention, and family involvement in treatment adherence and outcomes.

2. Priority research topics

The many presentations and the discussions at the conference, consistent with findings in the literature, identified that, in addition to opioids, the use of ATS (e.g., amphetamine, methamphetamine, and ecstasy) and ketamine are serious drug problems in Asia. HIV, HCV, and HIV/HCV co-infection resulting from injection drug use are prevalent and require special attention. Additionally, family involvement in patient care is a unique and important cultural factor influencing Asian communities and populations and should be included in the research agenda.

2.1. Neuroscience on HIV/HCV and ATS

This discussion was led by Drs Linda Chang, Gene-Jack Wang, and Betty Tai. The workgroup identified and discussed the following potential research questions:

- (1) *Different racial/ethnic groups have different morphometric measures (e.g., height, weight, proportions). Would it be useful to develop similar normative data resources for different ethnic/racial groups that can be used to evaluate future brain disorders, including drug exposure and drug abuse?*

An example of such a shared data resource is the NIDA-funded Pediatric Imaging Neurocognition and Genetics (PING) study (principal investigators: Chang, Dale, Ernst, Jer-nigan, Murray; RC2DA29475). This data resource provides a good example of this type of collaborative effort because it spanned many sites and quickly led to several high impact publications [2–5]. The study, which involved nine sites across the United States, collected data from approximately 1400 typically developing children aged 3–20 years, and the data are being shared with the neuroscience community. The biomedical and demographic data include family medical and drug use histories (if known), the National Institutes of Health (NIH) Toolbox (cognitive assessments), high resolution neuroimaging [including structural and diffusion magnetic resonance imaging (MRI) and functional MRI], saliva for DNA extraction and genome-wide association studies (GWAS), and drug usage data (from the PhenX Toolkit). These data of typically developing children across the ages provide a very useful normative dataset that allow scientific questions to be explored in a large pediatric population across the United States; in addition, future disease-based studies on this population can be compared and contrasted.

Another example is the IMAGEN study, which is a European research project investigating mental health and risk-taking behavior (including substance use) in teenagers [6]. The IMAGEN study is a multicenter genetic–neuroimaging investigation, with longitudinal follow-ups, of nearly 2000 14-year-olds and their parents from across Europe. The study has generated a valuable database for secondary analysis.

- (2) *Do tobacco smoking or drugs of abuse affect brain development or brain aging differently in the various racial/ethnic groups? What factors contribute to vulnerability to addiction to tobacco smoking across the different cultures or different countries?*

Dr Linda Chang's lab has examined the effects of prenatal cigarette smoking exposure and found that tobacco-exposed female infants show smaller brain volumes and more brain metabolite abnormalities than unexposed control females, whereas the male infants show no group differences [7]. Such sex differences were also found in rodent studies, which showed opposite effects of gestational nicotine on gene expression of myelin-related genes in adolescent male and female offspring [8]. These findings suggest that prenatal tobacco exposure may have lasting epigenetic influences in the brain structures or function of future generations. Given that tobacco smoking is popular in Asian regions, research should examine if tobacco smoking (or drugs of abuse) affect brain development in the various racial/ethnic groups, as well as factors related to vulnerability to addiction to tobacco smoking across different cultures or countries.

(3) *Which genes or factors contribute to the development of psychosis in psychostimulant users or other drug users? Are they different across the various racial groups? Are there tools that can be used or need to be developed cross-culturally to assess and treat psychosis?*

Genetic variations may account for the differential development of psychosis in psychostimulant users or other drug users. Genetic studies comparing various racial/ethnic groups (e.g., Asians versus Caucasians) will be extremely valuable. For instance, methamphetamine-induced psychosis is thought to be more common in Asia, based on earlier studies from Japan. Several single nucleotide polymorphisms [SNPs; e.g., in the A2A adenosine receptor gene (ADORA2A) and the serotonin 6 (5-HT₆) receptor gene] were found to be more prevalent in the Japanese population of methamphetamine-dependent individuals with psychosis [9,10], some with sex differences. However, whether such associations are also present in the Caucasian population is unknown. Having cross-national studies in order to compare findings may lead to new insights regarding methamphetamine-induced psychosis, which may have further implications for psychosis associated with other psychiatric disorders.

(4) *How do the different clades of HIV affect the brain? Anecdotal data show that Type C is less neurovirulent compared to Type B. Will they affect different racial/ethnic groups differently? Will these different effects be due to genetic variations? Does the same genetic polymorphism APOE- ϵ 4 have differential impact on brain disorders in different racial/ethnic groups?*

Dr Chang demonstrated how the apolipoprotein E (APOE)- ϵ 4 gene, which is known to increase the risk for the development of Alzheimer's disease in older individuals, may contribute to cognitive dysfunction and brain atrophy in HIV-infected individuals. In particular, younger HIV patients may show earlier expression of the deleterious effects of APOE- ϵ 4, with subcortical brain atrophy, whereas seronegative controls with the same gene may demonstrate larger brain volumes when they are young but show brain atrophy only in older ages (i.e., antagonistic pleiotropy) [11]. Because the effects of APOE- ϵ 4 may also be expressed differently in different racial groups (e.g., affecting Whites more than Blacks on working

memory and semantic memory [12]), such genetic variations or other factors could be explored across different racial/ethnic groups in Asia and the Western countries.

(5) *The use of marijuana is "very low" in some Asian countries (it is possible that it is underreported). Is this due to differences in genetic vulnerability or to different social/cultural pressures (e.g., is its very low use in Japan due to the strict laws there?). Are there different sensitivities to brain cannabinoid receptor Type 1 or Type 2 among Asians?*

The low prevalence of marijuana use in Asia also poses unique research opportunities. Social/cultural, genetics, and/or underreporting factors can be explored to learn more about this phenomenon.

2.2. ATS and mental health disorders

Led by Dr Rawson and Dr Compton, three areas of research are needed to address ATS and mental health disorders.

(1) *Genetic factors accounting for variations in psychosis and amphetamine use*

Abuse of amphetamines is widespread in API countries and populations. It has also been reported that many psychiatric patients use amphetamines. Some evidence suggests that genetic factors may account for variations in psychosis for individuals using amphetamines [13]. Research on the genetics of the response to amphetamine appears to have great potential to provide explanations for the differential response to amphetamine (persistence of psychosis, etc.) and changes in the brain produced by amphetamine.

(2) *What implementation models and strategies would provide the optimal method for addressing prevention and clinical services needs regarding amphetamines in Asia? What implementation models and strategies could best help integrate SUD services and other health services?*

Evidence-based prevention, treatment, and other services are much needed to address amphetamine use in Asia, but the optimal strategies to provide these services in Asia remain to be identified or developed. Additionally, integration of substance use disorder (SUD) services and other health services (e.g., for HIV) may also increase the likelihood of achieving favorable outcomes. Implementation research in these areas is needed to optimally address amphetamine and related problems in Asia.

(3) *What epidemiological research strategies can be best adapted to provide good data on the nature and extent of SUDs and HIV and identify the most critical populations?*

While epidemiological data on the nature and extent of SUDs and HIV in the Asia region have improved in recent years, there are still significant data gaps that limit these countries' ability to identify and understand the issues that need to be addressed. To provide good data on the nature and extent of SUDs and HIV, as well as to identify the most critical

populations, efforts are needed to identify, adapt, and apply the most appropriate epidemiological research strategies.

2.3. HIV/HCV transmission and social networks

Led by Dr Shoptaw and Dr Normand, several research ideas were suggested:

- (1) *Hepatitis B: Testing Truvada as treatment for HBV and PrEP for HIV in high risk HBV-positive MSM, particularly in Vietnam.*

Chronic hepatitis B is a global public health issue, with 350 million people worldwide infected with the hepatitis B virus (HBV)—75% of them in Asia [14]. HBV is the leading cause of chronic hepatitis in API countries, and up to 25% of these patients will eventually die of liver cirrhosis and its complications. HIV and HBV co-infection is also frequent in Asian countries, leading to increased morbidity and mortality in these regions.

Truvada is a HIV medication that prevents HIV from altering the genetic material of healthy CD4 cells, and thus prevents the cells from producing new virus and decreases the amount of virus in the body. It also has been approved as a pre-exposure prophylaxis (PrEP) for those confirmed to be HIV-negative and is used to prevent HIV among those at high risk for the infection, in conjunction with condoms and other safer-sex measures. Truvada has components that potentially can treat HBV, but it is not currently approved for the treatment of HBV, because its safety and efficacy have not been established. It was suggested that testing Truvada as a treatment for HBV and PrEP for HIV may be an innovative approach for high risk HBV-positive men who have sex with men (MSM), particularly in Vietnam.

- (2) *HCV/HIV: Combining surveillance and genetic sequencing in Taiwan among IDU networks.*

Another innovative research study that was suggested was to combine surveillance data with genetic sequencing among IDU networks. HIV and HCV are global public health problems, and the burden of these diseases is considerable. IDUs are at high risk for HIV and HCV infection and transmission. Globally, approximately 10 million IDUs are currently or have been previously infected with HCV, and four million are infected with HIV. East Asia is among the regions with the highest concentrations of HIV- and HCV-infected IDUs. Monitoring the distribution, evolution, and transmission of HIV-1 and HCV are critically important in efforts to prevent their spread.

Phylogenetic analysis of HIV and HCV viruses can be applied among infected IDUs to investigate the genotype distribution, evolution, and transmission of HIV-1 and HCV among drug users' networks. With globalization, the population migration between regions presents additional challenges to accurate and efficient surveillance. Therefore, international collaborative efforts are critical to address these important public health issues.

- (3) *SUD and infectious diseases: Studying community-based SUD treatment and infectious disease management in primary care settings.*

Despite the close connection between SUDs and infectious diseases, services for treating these disorders or diseases are often delivered by separate facilities or entities that are often disconnected. Outcomes might be improved by studying community-based SUD treatment and infectious disease management in primary care settings in, for example, Thailand and Los Angeles.

- (4) *Methamphetamine and HIV: Studying the brains of methamphetamine-using HIV-positive/negative people with a medication (ibudilast) that has strong anti-inflammatory properties.*

Another innovative idea is to test ibudilast among methamphetamine-using HIV-negative and HIV-positive people to study its effects on the brain. Ibudilast is an anti-inflammatory drug that may have some use in reducing methamphetamine addiction. Given that many methamphetamine-dependent users are at high risk for HIV, and HIV serostatus may complicate the response to the medication, it will be critical to study the brains of methamphetamine-using HIV-positive/negative people with this medication.

- (5) *Secondary data analysis on the SATHCAP regarding modeling of agent networks and spread of infectious diseases.*

The Sexual Acquisition and Transmission of HIV Cooperative Agreement Program (SATHCAP) is a multisite study that was funded by the NIDA and was designed to assess the role of drug use in the sexual transmission of HIV from traditional high-risk groups, such as MSM and drug users, to lower risk groups, such as non-drug-using sexual partners [15]. This database (accessible at <http://www.icpsr.umich.edu/icpsrweb/NAHDAP/studies/29181>) offers a great opportunity for secondary data analysis. A suggested example topic was to model agent networks and the spread of infectious diseases.

2.4. Additional topics: genetics, drug use prevention, and family involvement to improve treatment adherence and recovery

Noting that genetic studies potentially span the above topical areas, Dr Ming Li discussed smoking cessation to further illustrate the importance of genetic studies. Smoking dependence, like other types of addiction, is a world health problem that costs nearly six million human lives per year [16]. This is especially true in many Asian countries, where a majority of men report smoking on a regular basis, although relatively fewer women smoke cigarettes in Asia compared with the United States and European countries [17,18]. To identify genetic factors for smoking dependence, significant research efforts have been made by researchers from many countries throughout the world.

One of the most significant international collaborative efforts was a recently reported genome-wide meta-analysis of more than 140,000 participants for smoking, which revealed multiple loci associated with this behavior [19]. The primary reason for including so many samples in this study was due to the fact that smoking dependence is a complex disease that is

determined by many genetic loci, with a relatively small genetic effect for each locus. Therefore, in order to identify those susceptible loci with small effect for smoking dependence or any other addiction, thousands of samples are required. By contrast, there is no single research team that is able to collect so many participants from different geographical locations. Thus, this requires researchers from different institutions to work together on a scientific problem with a common interest. For example, the genetics study mentioned above consisted of many authors representing many different institutions and countries. In addition to the large sample size required for a genetic study, genetic differences among different ethnic populations also require researchers from different countries to collaborate with each other. Although some common susceptible loci have been identified for smoking dependence across different ethnic samples in the past, a significant number of loci appear to be ethnicity-specific. For example, the association of smoking behavior with several loci in the nicotinic receptor subunits alpha 5, alpha 3, and beta 4 gene cluster on chromosome 15 identified from European populations [20–22] appears to be less significant in participants of African and Asian origin [23–25]. Again, this points to the significance of collaboration among researchers from different institutions and countries.

Further, we would like to point out although most researchers realize it is important to do collaborative research, its execution might not be as easy as it sounds. Many practical issues such as language differences in scales and measures, Institutional Review Board (IRB) issues, DNA sharing, and authorship could arise when one tries to set up such collaborations among researchers from different institutions across different countries. However, all these issues can be resolved with careful planning and discussion.

Another important research topic is substance use prevention in Asia. Prevention is a cost-effective approach to improve public health. Yet, very little prevention research for SUDs has been explored or conducted in the Asian region. Both resources and infrastructure in the Asian region are needed to allow the development of SUD prevention research. During this conference, it was proposed that the development and application of culturally appropriate SBIRT (screening, brief intervention, and referral to treatment) in primary care settings may be needed in API countries.

Numerous studies have demonstrated the importance of social and family support with regard to patient treatment compliance and outcomes. Culturally, family factors or support are highly salient in every aspect of life in Asian communities. Although research studies are limited, there have been some observations that family involvement may be a major factor contributing to the superior retention rate for patients participating in methadone maintenance programs in Vietnam. Further research may be fruitful to test family involvement-supported interventions that improve treatment adherence and recovery in Asian countries.

3. Conclusions

The exciting research topics and suggestions shared in the conference are encouraging and will form the bases for the

formation of several workgroups and the planning for future collaboration in cross-national studies in Asia. It is expected that these workgroups will stimulate collaborations that will eventually lead to research studies addressing critical substance abuse and HIV problems common across the Asian countries and, at the same time, advance the scientific knowledge of substance abuse and HIV infection.

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