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Plenaries

KN01

Building Global Capacity for Aging Mental Health Research

Mary Sano, *Alzheimer's Disease Research Center, United States*

The International Psychogeriatric Association (IPA) and its members have a long history of developing global alliances to move forward the cause of geriatric mental health. Among its many accomplishments, the association members have worked to establish a common diagnostic language particularly in the area of dementia and its behavioral disturbances, an international consensus on capacity and consent, guidelines on evaluation of geriatric mental health and harmonization of guidance for regulatory approval of dementia therapeutics. There is still much to be done, including building work force capacity, technology infrastructure, international consensus on dementia prevention designs, and the development of a common language of relevant outcomes to demonstrate effective interventions to improve and maintain geriatric mental health.

This presentation will review the success of several international collaborations that address these areas. The International Consortium for the treatment of dementia in Down Syndrome will provide an example of developing clinical research expertise within care centers around the globe to achieve registration level data collection for clinical trials. Efforts to expand normative data collection for cognitive characterization of aging across multiple cultures will be described. These provide the basis for defining normal cognition and the earliest transition to cognitive impairment. Such normative knowledge is a minimum requirement for designing dementia prevention studies. New projects to define behavioral and mood disturbances will be summarized which look to the unique international expertise of IPA and its affiliates to create a common diagnostic entity with clinical meaning and relevance to the global community. Finally remaining challenges will be defined including the need to focus on disease prevention. These require definitions of positive health states for which to strive. Focus on the prevention of dementia and delaying the transition to cognitive impairment or on the avoidance of recurrence of mood and behavioral disturbance is an important aspect of disease prevention to insure mental health and wellness. Designing studies to make this a reality will require broad acceptance of new technologies for detection of risk and prediction of disease. It will also require a workforce skilled in sophisticated neuropsychological evaluation, neuroimaging and genetics. Proposals will be offered for standardizing diagnoses and outcomes and extending what we have learned in other international trials in geriatric mental health. Emerging technologies including imaging and genetics can also be shared internationally to insure that all countries and regions have the capacity to fully participate in trials for early detection and novel, biologically based therapeutic interventions. Proposals for expanding international consensus projects to define behavioral and mood disorders of aging along with workshops to train providers in the use of research diagnostic schemes offer the opportunity to insure that aging mental health is truly a global initiative. We will conclude with a panel of experts who will share their perspective on how we can move this agenda forward.

PL01-01

How early can we diagnose Alzheimer's disease?

Ronald Petersen, *Alzheimer's Disease Research Center, Mayo Clinic College of Medicine, United States*

Objective: With the new criteria for the Alzheimer's disease (AD) spectrum, the role of biomarkers has been expanded, but the criteria have not been validated.
Method: The Mayo Clinic Study of Aging is a population-based longitudinal project recruiting subjects ages 50 to 90 years. The subjects are not demented and are randomly sampled from the community and receive a complete clinical evaluation involving a nurse, a physician who performs a mental status evaluation and a neurological examination and a neuropsychologist. The subjects are diagnosed by consensus using published criteria and are followed longitudinally. Neuroimaging biomarkers are obtained on a large subset of the subjects but are not used in the diagnostic process.
Results: Since 2004, over 3000 subjects have been evaluated in the Mayo Clinic Study of Aging. There were two cohorts recruited: The original

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cohort ages 70–90 has been followed for up to eight years, and the younger cohort ages 50–69 years has been followed for approximately one year. The subjects have been classified according to their neuroimaging characteristics of being amyloid positive or negative and neurodegeneration positive or negative. Neurodegeneration is evaluated by quantitative MRI and/or FDG PET. In general, approximately 30% of the cognitively normal subjects are amyloid positive, and the progression rate to MCI increases as one goes from stage 1 to stage 3 in using the new criteria for preclinical AD. **Conclusion:** The criteria for the AD spectrum appear to work reasonably well in the general population. However, there is a group of subjects that were found to be amyloid negative and neurodegeneration positive, and these individuals were not included in the new criteria.

PL01-02

New understanding of γ-secretase action and surrogate marker for pathological amyloid processing—Early intervention against Alzheimer's disease

Masatoshi Takeda, *Department of Psychiatry, Osaka University, Japan*

Experience of donepezil, galantamine, rivastigmine and memantine has now demonstrated limited clinical usefulness to Alzheimer's patients, because the patients may show the cognitive decline below the baseline after one year continuous use of these symptomatic drugs. Disease-modifying drugs to slow down or suppress the pathological process of the disease is highly expected. The development of disease-modifying drugs, however, has not been successful despite of the continuing endeavor in these 20 years. Many compounds, including gamma-secretase inhibitors, and gamma-secretase modulators, failed to produce good results in clinical trials. The results of the clinical trials of immunotherapy for Alzheimer's disease were released last summer with disappointing results. Considering these situations, there is a pessimism concerning the development of disease-modifying drugs under the present system of the clinical trial.

New style of clinical trials of disease-modifying drug for Alzheimer's disease is proposed and discussed, in which the reduction of the conversion rate from MCI to dementia could be used as the primary outcome of the clinical trials.

Establishment of biomarkers for early detection of possible patients is necessary and our data of APLP1 and APLP2 peptides will be discussed as the surrogate marker for pathological gamma-secretase activity.

PL01-03

Imaging and diagnosis of prodromal Alzheimer's disease in patients with mild cognitive impairment

Karl Herholz, *Clinical Neuroscience, Wolfson Molecular Imaging Centre, University of Manchester, United Kingdom*

Dementia is the end stage of a process of accumulating brain damage which is progressing for several decades before the clinical symptoms become apparent. While there is little chance for efficient therapy of manifest dementia other than temporary symptomatic improvement, early intervention could possibly prevent or delay its onset. Thus, there is a need for diagnosing Alzheimer's disease (AD) before actual onset of dementia.

Mild cognitive impairment (MCI) can be an early stage of AD, but there are also patients with MCI who will not progress to AD, and some may even revert back to normal. Patients with dense memory deficit who fulfill criteria for amnestic MCI and carriers of the apolipoprotein E4 allele are at particularly high risk for developing dementia. In addition, modern imaging techniques can identify patients with AD at this stage. The most advanced technique is amyloid imaging by positron emission tomography (PET), with suitable fluorine-18 labelled tracers now becoming commercially available. It can identify fibrillary amyloid deposits, which are pathological marker of AD, up to 20 years before onset of dementia. Patients with MCI and a positive amyloid scan have a risk of approximately 50% to progress to dementia within 2 years. PET with 18F-fluorodeoxyglucose (FDG) can identify MCI patients who already have neocortical synaptic dysfunction, which is another indicator of impending dementia. Hippocampal atrophy, which is closely related to the typical memory deficits of AD, can be measured by volumetric magnetic resonance imaging (MRI). MRI can also detect changes in white matter. Vascular lesions seen on T2-weighted scans indicate and increased risk for developing dementia, and changes in fibre integrity seen on diffusion tensor imaging (DTI) can be associated with AD. Resting-state functional MRI is a sensitive technique to detect changes in large-scale cortical networks at a very early stage.

These techniques are now becoming increasingly available to support the diagnosis of prodromal AD

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in patients with MCI, and are also being employed as inclusion and outcome parameters in clinical intervention trials.

PL02-01

Complexity and dementia—the challenge of multimorbidity

Sube Banerjee, *Dementia, Brighton and Sussex Medical School, University of Sussex, United Kingdom*

Complexity is the rule rather than the exception in dementia. People with dementia by definition have multiple challenges in multiple domains as a consequence of their dementia. In addition less than a fifth of people with dementia only have dementia. Four fifths have at least one other significant physical or mental disorder and many have a number of conditions simultaneously. Multimorbidity in those with dementia is therefore common. Many of our existing research and management paradigms are based on the notion of simplicity (i.e., addressing the dementia alone) or have a presumption of additiveness (i.e., that the treatment of Condition X in dementia is simply the treatment of Condition X and the treatment of dementia). Emerging evidence suggests that there may be considerable error in making these assumptions and that failing to deal with complexity means failing those with dementia. In this session we will consider complexity and multimorbidity in dementia and what this means in our mission to improve the quality of life of people with dementia and those that support them by improving the quality of care that we provide.

PL02-02

Current status of mental health of the Korean elderly predicting its future

Maeng Je Cho, *Seoul National University, Korea*

South Korea is the most rapidly aging society among the OECD countries. The proportion of the elderly to the rest of the population was a mere 2.9% in 1960, 11.0% in 2010, is predicted to be 24.3% in 2030, and 40.1% in 2060. Accordingly, the burden of the rapid aging population is not only of a socio-economic nature, but also one of health related concerns. Among the many old age health issues, elderly mental health problem is one of the most disturbing and disabling health conditions. There is some characteristic pattern prevalence estimate of mental disorders in Korea; higher prevalence of Alzheimer's dementia, coupled with lower prevalence of depressive disorder than other Western countries. The lecturer presents the present mental health status of the Korean elderly, and tries to predict future problems caused by this. He also discusses the current and coming mental health issues such as research & policy making of services empathizing the cross-cultural point of view.

PL03-01

Hormones and the aging mind

John Morley, *Division of Endocrinology, Department of Internal Medicine, Saint Louis University Medical Center, United States*

With aging there is a decline in many hormones. The majority of older persons have low vitamin D levels and these may be particularly low in persons with Alzheimer's disease. Vitamin D stimulates neurotrophin release and decreases brain inflammation. Vitamin D receptors are associated with abnormal executive function and depression. Low testosterone in males results in decreased libido, poor erections and decreased strength. In addition, testosterone improves some aspects of memory and low testosterone is associated with rapid conversion from mild cognitive impairment to Alzheimer's disease. Testosterone also improves energy and decreases dysphoria. Animal data has shown effects of growth hormone on neurogenesis but we showed that a growth hormone receptor antagonist improves memory. Low IGF-1 is associated with severity of delirium. Pregnenolone and DHEA are potent enhancers of memory in mice but results in humans have been disappointing. Many hormones have been shown to modulate the anorexia of aging. While hormones are clearly not the modern function of youth appropriate use may improve some physical and mental functions.

PL03-02

Sex-specific responses to anti-aging therapies

Steven N. Austad, *University of Texas Health Science Center, United States*

Men and women experience aging differently. In virtually every technologically developed country, women live longer, but despite their survival advantage have poorer health throughout life as measured by days sick, number disabled or incapable of living independently in their later years. Surprisingly, in experimental animals for which

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senescence-retarding genetic or pharmacological interventions have been developed, there are also widespread sex differences in the response to these interventions. At least 6 genetic manipulations that substantially increase longevity and health in mice work only in one sex. Sometimes it is males that are affected by the treatment, sometimes females. Similarly, 4 of 5 pharmacological treatments that extend life in mice affect only one sex. Sex specific differences in components of health are also widespread in these interventions. This talk will describe these sex-specific differences, discuss their implications for human medicine, and suggest research paradigms for their investigation.

PL03-03

Anatomical reference system in neuroimaging, and neurodegenerative diseases in high field magnetic resonance images

Je-Geun Chi, *Seoul National University, Korea*

In recent years thanks to the advance of neuroimaging technology with drastically increased resolution, the sectional images of the central nervous system became the main source of neurological information. An accurate identification of cerebral structures is necessary for quantification of computed tomography, magnetic resonance imaging and positron emission tomography.

We have developed an anatomical localization system that accounts for individual brain shape and size by using the proportional grid system. The line connecting the centers of the anterior commissure (AC) and posterior commissure (PC), central intercommissural line (CIL), is the base line for the coordinate system, being the midpoint (brain center) of AC and PC to be the zero point for x, y, and z axis. X-axis is defined by CIL.

The horizontal plane is defined as an axial plane, x-y plane, which contains the AC-PC line at the center, with a positive sign superiorly and a negative sign inferiorly. Similarly, for the coronal plane, x-z plane is assumed, and those planes anterior to the zero point are set with a positive sign, while posterior planes are noted as negative. For the sagittal images, y-z plane, those at the left side are set as negative while those at the right are denoted as positive. The median image is set with the longitudinal cerebral fissure as the origin.

The availability of an accurate standard intracerebral reference line for overall neuroanatomy will enhance the standardization of image interpretation of any given section of the brain so that the information obtained can be compared easily. Moreover, such information will be advantageous for stereotactic surgery including deep brain stimulation.

In addition we would like to share some images of critical anatomical structures in neurodegenerative diseases, such as hippocampus, substantia nigra, subthalamic nucleus, together with thalamo-limbic fiber system seen with ultra-high field magnetic resonance imaging and tractography, obtained through 7.0 Tesla MRI in vivo.

PL04-01

Neurocognitive disorders and Alzheimer's disease in the DSM-5

William E. Narrow, *Division of Research, American Psychiatric Association, United States*

Objective: The fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was released in May, 2013. Significant changes were made to the former DSM-IV chapter entitled, "Delirium, Dementia, and Amnestic and other Cognitive Disorders."
Method: New features contained in the DSM-5 Neurocognitive Disorders chapter will be outlined, including new diagnostic concepts, changes to diagnostic criteria, and the rationales for change. Particular attention will be paid to neurocognitive disorders due to Alzheimer's disease. Data from the DSM-5 field trials on reliability, feasibility, and utility of the neurocognitive disorders will be presented.
Results: Dementias and amnestic disorders are now grouped into the category of "major neurocognitive disorder" in DSM-5, and mild neurocognitive disorder is a newly introduced concept. Diagnostic criteria and accompanying text for major and mild neurocognitive disorders due to Alzheimer's disease were revised to reflect rapidly accumulating research evidence and consensus criteria developed by other expert groups. For example, the use of a relevant genetic mutation as a diagnostic criterion is now permitted. In the DSM-5 field trials, test-retest reliability was very good for major neurocognitive disorder and good for mild neurocognitive disorder. There were issues in the field trials concerning the use and choice of neuropsychological tests for diagnostic purposes.
Conclusion: The Neurocognitive Disorders reflect the DSM-5's aim to be clinically relevant and to reflect current research. The new concepts in this chapter will be further evaluated as DSM-5 is put into clinical and research use. Future versions of

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DSM should be able to readily incorporate further research advances, such as the development of new diagnostic tests, into the diagnostic criteria.

PL04-02

Evolving concept of Alzheimer's disease: Challenging issues of diagnosis and treatment

Charles Decarli, *UC Davis Alzheimer's Disease Center, United States*

As the human lifespan continues to lengthen, Alzheimer's disease has become a world-wide public health concern. Initially believed to be a rare cause of dementia amongst the very young, Alzheimer's disease is now considered the leading cause of dementia and the focus of extensive medical research. The major aims of this research are based on the amyloid cascade hypothesis and the concept of a prodromal phase of the illness lasting 10 to 20 years. Basic science research has identified the molecular pathways of amyloid metabolism, including the most recent discovery of "tau seeding" that may explain progression of the disease once amyloid neuronal toxicity has occurred. Results from this research have led to the development of medications to modify specific pathways associated with amyloid creation or the more novel anti-amyloid antibody treatments. Despite these efforts, clinical therapeutic trials have consistently failed to identify medications that are capable of modifying the course of the disease. The cause for these failures is uncertain, but one hypothesis poses that, in order for anti-amyloid treatments to be effective, they must begin at the earliest stages of the disease, including possible treatment of asymptomatic individuals at increased risk for dementia due to the presence of an abnormality determined by biomarker study. An array of biological markers is now available and a widely accepted model of sequential changes in these measures exists. This biological model is also a principal component of newly developed clinical criteria that emphasize both preclinical and prodromal states of Alzheimer's dementia. Accurate biological markers will be essential to selection of subjects for such trials. In my presentation, I will discuss the current state of research involving biological markers and clinical trials currently designed to treat individuals at high risk for Alzheimer's disease. In addition, I will discuss the potential impact of the routine use of biological markers, particularly amyloid imaging in clinical practice.

PL04-03

Prevalence of tau aggregation pathology in Asia

Claude Wischik, *TauRx Therapeutics Ltd, United Kingdom*

Objective: TauRx is conducting the first Phase 3 trial testing Tau Aggregation Inhibition (TAI) using LMTXTM as a treatment for Alzheimer's disease (AD). We have developed a model to estimate prevalence of brain Tau pathology in Asia for the period 2010 - 2050 based on WHO population projections, Chinese cognitive decline data and European estimates of age-specific Braak stage transition probabilities.
Method: Post-mortem data from 847 cases spanning ages 45 - 95 (Ohm et al., 1995) were used to estimate age-specific Braak stage transition probabilities. Survival probabilities by age and MMSE cut-off were calculated from a UK-based community study in 13,000 subjects aged 65 and above (MRC CFAS, 1998). Similar age-specific survival probabilities were calculated from a Chinese community study (Nation-Wide Healthy Longevity Survey, 1998–2012, Yi Zeng et al.) in 2,373 subjects aged 60 - 105.
Results: The age-specific survival probabilities for MMSE cut-offs of 26, 20 and 14 (conventional segments for mild and moderate dementia) are very similar in UK and China, suggesting similar underlying biological substrates for cognitive decline. Applying European Braak stage transition probabilities to Chinese and Asian demographic data suggests that, like Europe, 49% of the Asian population aged 45 or over have some degree of brain Tau pathology. We estimate that in Asia this is comprised of 28% at Braak stage 1 (293 million), 10% at Braak stage 2 (106 million), 8% at Braak stage 3 (87 million) and 3% at Braak stage 4 or beyond (34 million). Those at Braak stage 4 or beyond are expected to increase 4-fold by 2050.
Conclusion: As the spread of Tau aggregation pathology is now known to be a prion-like in the brain, there is an urgent need to test and deploy TAI-based preventative treatment in Asian populations.

PL05-01

Dignified aging and the future of old age

Cees Hertogh, *General Practice & Elderly Care Medicine, VU University Medical Center Amsterdam, The Netherlands*

In today's discourse on aging, dignity has become a very popular notion. We read about aging with

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dignity and the term is frequently used in connection with end-of-life-care. Its frequent use however contrasts highly with the (lack of) clarity of the term. According to some ethicists, appeals to dignity are often vague statements or mere slogans that add nothing to our understanding of the topic. Some even contend, that 'dignity is a useless concept'. In this respect it is not without relevance to note, that reference to dignity is often made in situations of indignation and dissent, when it is felt that a state of affairs or a certain type or behavior are unworthy and in conflict with human dignity. This raises the question why so many people appeal to dignity and belief they are referring to a honorable concept.

Indeed, the term dignity refers to an ambiguous concept, an ambiguity that is at least threefold. First of all there is the customary difficulty of defenders of dignity to define the concept they appeal to. The second is that, although international human rights frameworks state that dignity is intrinsic to humanity as such and therefore inalienable, many contemporary debates on dignity refer to situations in which human dignity is felt to be undermined or is even lost. In Western societies, dementia and the situation of an old age in dependency are frequently mentioned as examples of a human life exempt of dignity. As a third ambiguity there is the challenge for defenders of the concept to reconcile the idea of dignity as an inalienable value with the stigmatization of certain conditions and situations as radically undignified. These ambiguities call for an alternative concept to guide us in developing feasible research policies and research agendas for the future of old age.

PL05-02

Challenges of ageing with dignity for older people with mental disorders in China

Helen Fung-Kum Chiu, *Psychiatry, The Chinese University of Hong Kong, Hong Kong SAR PR China*

China is developing rapidly economically. At the same time, the population of China is ageing at a very rapid pace. In 2010, 14% of the population is aged 60 or above and this will increase to 25% by 2030. In 2013, there are an estimated 202 million older persons in China, and two-third of the older population live in rural areas. Apart from the very rapid ageing of the population, another phenomenon in China is the vast number of internal migrant workers, who are young people from rural areas migrating to work in urban areas. The current population of internal migrant workers in China is estimated to be over 200 million. The massive exit of the young people from the rural areas has led to the phenomenon of a sizeable population of "left-behind elders" in the rural areas. The above 2 features pose great challenges in the care of older people in China, especially in the rural areas which lag behind the urban areas in health care and social services. Indeed, the elderly suicide rate in rural areas is very high and is 4 to 5 times higher than the elderly suicide rate in urban areas. The prevalence of dementia in China is estimated to be 3% for people aged 60 years or above. Due to the enormous elderly population in China, this translates to a great number of people with dementia.

This lecture will explore the challenges of care of older people with mental disorders in a transitioning China, and will examine some models of mental health service provision for these older people in China.

PL06-01

Lessons learnt from studying depression in late life

Ranga R. Krishnan, *Duke-NUS Graduate Medical School, Singapore*

The purpose is to understand the aetiology of late life depression and its treatment.

Genetic factors are less important in late onset depression but medical conditions and social factors including subjective social support and life stressors appear to be more important.

The age of onset of depression relates to vascular risk. Vascular risk factors increase the risk of late onset depression. One mechanism by which they increase the risk is by damage to the prefrontal circuit that mediates mood regulation. This type of depression due to vascular factors is called vascular depression. MRI of the brain is used to identify these patients. These patients often have a more difficult course with increased morbidity including dementia and increased mortality. There are few studies that are designed to specifically treat vascular depression. Nimodopine in two small studies has shown some efficacy.

PL06-02

Cognitive impairment and cognitive decline in late life depression

David Steffens, *Psychiatry, University of Connecticut Health Center, United States*

Major Depression in older adults has long been associated with a characteristic neuropsychological

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profile, including executive impairment, difficulties with concentration and attention, and slow speed of information processing. The term "depression-executive dysfunction syndrome of late life" has been used to describe the combination of mood and cognitive symptoms among older depressed adults. Recent studies have also focused on the presence of memory impairment in geriatric depression, demonstrating that memory problems may persist after successful treatment of mood symptoms.

Epidemiological research has linked depression with subsequent cognitive decline and dementia, including Alzheimer's disease. More recent clinical studies have sought to identify clinical and biological factors related to progression of cognitive decline among older depressed adults. Risk of cognitive decline and dementia has been associated with severity of executive and memory impairment, worsening of cerebrovascular disease on brain imaging, and severity of psychosocial stress.

This session will review recent findings related to cognitive impairment and cognitive decline in major depression, explore factors related to development of dementia among older depressed adults, and discuss future direction for research in treatment and prevention of dementia in geriatric depression.

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