

China is Prepared to Fight Against Emerging Mental Health Disorders?

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ABSTRACT: *Over past three decades a rapid change in social and economic development has been made in China. As a result of the modernization, mental health disorders have surpassed cancer and the cardiovascular diseases and become the leading cause of burden. However, the large demand and inadequate access to mental health services are big challenges to the mental health care. China has passed the first mental health law in late 2012, and recently announced the national five-year mental health work plan. Autism, schizophrenia, depression and dementia, four brain disorders occurring at different stages across the lifespan, are considered as prioritized disease areas. These diseases are emerging mental health issues, and efforts to scientific research may provide important implications for neuropsychiatric medicine, in particular for developing novel strategies for effective therapeutic and preventive intervention, to fight against mental health disorders in China.*

BACKGROUND

A rapid change in social and economic development has been made since adopting the opening and reforming policy in late 1970. This is characterized by a fast economic growth, massive relocations or migrant workers from the rural to the urban areas, and low fertility rate which is partly caused by the implementation of family planning policy, in particular by promotion of deferred marriage and childbearing, fewer but healthier babies (Peng, 1998), and by more strict “one-child policy” in the urban areas (Banister, Bloom & Rosenberg, 2010). In the middle of 1990s, the fertility has already declined to below the replacement level, 2 children per woman (Peng, 1998), and since then has remained below this level for almost 20 years. According to the Migration Information Source of the Migration Policy Institute (January 4, 2012), in 2011 there were an estimate of 145 million rural-urban migrants which accounts for about 11% of the total population in China.

As a result of the modernization processes and the early health care movement fighting against epidemics of infectious diseases, China has experienced an epidemiological transition from the infectious to the chronic diseases in much shorter time than many other countries (Cook & Dummer, 2004). However, the urbanization has created new health problems, as non-communicable diseases such as cancer and cardiovascular diseases have emerged as a health concern in both urban and rural areas (Zhu et al., 2011). The burden of chronic diseases has increased the health-care cost substantially (Yang et al., 2008). Meanwhile, the urbanization tend to be with a fast-paced lifestyle and competitive working environments that may cause elevated psychosocial stress and affect many individuals with psychological and behavioral problems in particular migrants (Chen, 2011; Cui, Rockett, Yang & Cao, 2012). This, if lack of access to health services, may lead to an increase in chronic diseases including mental health disorders (Abbott, 2008). It is shown that urban upbringing is associated with elevated cortisol responses to acute stress, suggesting a change in (re)activity in the hypothalamic pituitary adrenal (HPA) that have implications for multiple psychiatric disorders (Faravelli et al., 2012).

While not the leading cause of death, mental health disorders have surpassed the cardiovascular diseases and cancer, and become the leading cause of burden in China. In a survey conducted in four provinces (Shandong, Zhejiang, Qinghai and Gansu) of China from 2001 to 2005, the estimate of 1-month adjusted prevalence of any mental illness in adults aged 18 years or older was about 17.5%, and 1% was for psychotic disorders (Phillips et al., 2009). There are 170 millions of adults with at least one type of mental disorders, and 10% of which have serious mental disorders (Phillips et al., 2009; Qian, 2012). However, more than 90% of patients with severe mental disorders have not been properly treated with medications (Qian, 2012). This would be a huge demand for mental health services in China. According to the Global Disease Burden study, mental health and behavioral disorders, substance use and musculoskeletal disorders account for almost half of the years lived with disability (YLD), an indicator that measure the burden of chronic diseases (Yang, Wang et al. 2013).

Development of Mental Health Services in China

The mental health services and resources are very limited throughout the 20 century due to historical reasons. While the formal mental health work dates back to more than 100 years ago when the first western style psychiatric hospital (currently the Guangzhou Brain Hospital) was established in 1898 by an American missionary, John Kerr (Liu et al., 2011), the development of mental health facilities was very slow until 1950 when large psychiatric hospitals started building at provincial level. In 1958 the community mental health work began in five regional centers in Shanghai, Beijing, Hunan, Sichuan and Jiangsu to provide professional trainings and develop treatment and prevention plan for psychosis (Liu et al., 2011). Unfortunately, the community mental health work was disrupted during the Culture Revolution (1966-1976), and later the economic reform started late 1970s that also destructed the overall community health care system.

Overall the mental health work had largely remained little change until late 1990s when the central government started paying attention to it. In 1999, an important workshop was convened by the central Chinese government and the World Health Organization in Beijing calling for the governments at all levels in China to strengthen the leadership and support for mental health care, and to respect patients' right. Two years later, the first national mental health work plan (2002-

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2010) was announced by the Ministries of Health, Public Security and Civil Affairs and the China Disabled Persons' Federation (CDPF). Almost at the same time, the China Center for Disease Control and Prevention (China CDC) was established in 2002, and the China CDC's Mental Health Center was also announced to build based on Peking University Institute of Mental Health to coordinate the national mental health work and provide technical guidance for mental health across the country. Following the first national mental health plan, the Ministry of Health along with other departments of the State Council announced the Guidance for the National Mental Health Development (2008-2015) in 2008. All these efforts made by the central government led to that the National People's Congress of China pass the first mental health law (http://www.gov.cn/jrzq/2012-10/26/content_2252122.htm) in late 2012, with specific focus on promoting psychological well-being, making diagnosis and providing necessary treatment of mental health disorders, and protecting lawful rights and interests of patients (Chen et al., 2012). The mental health law enactment marks an important progress in the mental health work.

The mental health service resources are hard to meet the demand for mental health care. Psychiatrists and psychiatric nurses are major health professionals providing mental health services in China. Most of them are with mental health hospitals, and there are very few clinical psychologists, psychotherapists and social workers. In 2004, there were 1.24 licensed psychiatrists and 1.91 psychiatric nurses per 100,000 populations, which is far below the average of 4.15 psychiatrists and 12.97 psychiatric nurses per 100,000 populations (Liu et al., 2011). Meanwhile, as of early 2015, the number of psychiatric beds is about 1.71 per 100,000, which is also below the global average of 4.36 (Liu et al., 2011), and two-thirds of counties have no professional institutions for mental health services, according to Mr. Guoqiang Wang, the vice Chairman of the National Health and Family Planning Commission of China, at a speech on the National Mental Health Integrated Management pilot start video conference (Jian Kang Bao, *Health Daily*, June 12, 2015). These resources are mostly located in the urban areas, very little available in the rural areas. There is a huge disparity among geographic regions from more developed eastern to the less developed western China. In addition, the low rate of public awareness is another issue preventing patients or their families from seeking for mental health services. Building mental health infrastructures and increase the trainings of specialized mental health workers will be the priority for the mental health care.

The National Mental Health Work Plan (2015-2020)

China begins to pay more attention to mental health care by announcing the second national mental health work plan (2015-2020). On June 4, 2015, the General Office of the State Council announced the national five-year plan for mental health made by the National Health and Family Planning Commission of China (http://www.gov.cn/zhengce/content/2015-06/18/content_9860.htm). The goals of the mental health work plan are by 2020 to 1) further improve the mechanism for integrated management and coordination of mental health services at all levels of province, municipality, county, as well as 70% of townships; 2) essentially complete the establishment of mental health service systems and networks at province, municipality and county level; 3) preliminary overcoming the shortage of specialized mental health professionals, the average number of psychiatrists and mental health professionals reach from 2.8 to 4 per 100,000 population in different regions across the country; 4) assure that rescue and management tasks for severe mental disorders are effectively implemented, the rate of registration and management for severe mental disorders reach 80% and treatment rate for patients with schizophrenia more than 80%; 5) significantly increase the treatment of commonly seen mental health disorders and psychological behavior problems, in

particular to increase the therapeutic treatment rate of depression by 50% from its current level; and establish a rescue hotline at every province and 70% of municipalities; 6) begin to establish the models for rehabilitation services for patients with mental health disorders, through integrating all level of professional mental health services with community- and family-based supports; and 7) significantly improve the social environment for mental health work. These are more specific goals for the governments to archive over next five years in order to improve mental health services in China.

To achieve the goals of this plan, a focus should be on building physical infrastructures for mental health at county and community level, increasing the trainings of mental health professionals, and promoting health education to increase the awareness of commonly seen mental health disorders and psychological illness. While the mental health infrastructure has improved greatly over past decade, so far two-thirds of counties have no specialized mental health institutions. County is an important administrative level in China. An establishment of specialized department of psychiatry is necessary at county hospital to provide clinical diagnosis and treatment or technical support for mental health services. Meanwhile, mental health department should also be established at the county's Center for Disease Control and Prevention to promote mental health education so to increase the awareness of mental disorders and psychological behavior problems, and to coordinate the mental health services at community level. This should also include the establishments of psychological counseling, rehabilitation centers for mental health and social workers at county and community level. The establishment of community mental health services will reduce the huge disparity of mental health services between the rural and urban areas.

Increase in financial support for mental health services and for scientific research on mental health disorders has also been stressed as safeguard measures to archive the goals of the mental health work plan. Basic and clinical research have been emphasized on schizophrenia, the most severe mental health disorder, along with commonly seen mental health disorders and psychological behavioral problems in the fragile populations of children and the elderly. Epidemiological study of mental health disorders and related health policy research are needed. Finally in the safeguard measures of the plan, multidisciplinary researches on biological, psychological and social determinants of mental health disorders, as well as translational psychiatric research are particularly mentioned. These allow us to systematically examine the etiology of mental health disorders and identify risk factors to develop novel therapeutic treatment, effective prevention and intervention strategies. Scientific research can greatly help us to fight against the mental health disorders effectively. Autism, schizophrenia, depression and dementia, four disorders occurring at different stage across the lifespan, are of focus.

Autism

Autism is a highly heritable childhood neurodevelopmental disorder with unknown etiology. It manifests with impairment in language communication, social interaction and responsiveness, and restricted and repetitive patterns of interest or behaviors (Bailey, Phillips & Rutter, 1996). Autism presents in the first 3 years of life, and the diagnosis of autism is made more frequent in boys than girls. While lack of a national representative estimate (Sun et al., 2013), the prevalence of autism has likely increased in China. According to the US Center for Disease Control and Prevention, 2% of US school age children are reported to have autism (Blumberg, Kogan, Schieve & Jones, 2013). Owing to lack of effective therapeutic treatment, most of families with autistic children have to rely on family care or turn to the limited special education programs. The total estimate of direct and indirect cost for autism is not much less than that in

the United States (Ou et al., 2015). The worst case is that we do not know what cause the disease. Although autism is highly heritable, searching for inherited common genetic variants has not been quite fruitful. Only a few common genetic variants have been associated with autism (Wang et al., 2009; Anney et al., 2010; Xia et al., 2014), although recent studies provide evidence that most genetic risk of autism resides with common variants which act additively (Klei et al., 2012; Gaugler et al., 2014). Very few epidemiological studies have been carried out to find environmental factors that contribute to the risk of autism in China.

Autism is a neuropsychiatric condition that is relatively new to both the public and clinical psychiatrists in China. The tools commonly used for making diagnosis such as Autism Diagnostic Observation Schedule (ADOS), the Autism Diagnostic Interview-Revised (ADI-R) and other screening instruments in the Western society are still lacking of validation in Chinese (Guo et al., 2011; Sun et al., 2014). In 2011, the first national autism research program was awarded, with 30 investigators from psychiatry, genetics and neuroscience together, to the study of autism in China. Within this program, formal group trainings on ADOS and related diagnostic tools were conducted for clinical investigators from several leading institutions in childhood psychiatry. Making efforts to enhance clinical trainings and increase the public awareness of autism are essential for early detection and necessary intervention.

Clinical and etiological study of autism is very important at the current stage. Determining the distribution of disease and identifying genetic and environmental factors associated with the risk of autism will contribute to the understanding the disease biology. This would be the key to the development of novel therapeutic treatment and intervention for autism. Currently the diagnosis of autism is made based on some subjective behavioral and observational tools. Discovery of molecular biomarkers will contribute to the improvement of clinical diagnosis of the disease (Wang et al., 2015). The development of effective therapeutic treatments and promotion of special care and trainings for families with autism may play an important role in the prognosis of children with autism.

Schizophrenia

Schizophrenia is a severe brain disorder affecting 1% of worldwide populations. It presents with a collection of signs and symptoms, primarily starting paranoid delusions and auditory hallucinations in adolescence or early adulthood, and often with cognitive deficits. The peak age of onset is between 18 to 25 years, and no gender difference in the rate of diagnosis. Despite that the study of schizophrenia has been over a century, we are still not clear about what cause the disease. There is no effective pharmaceutical treatment even that the medication has been applied more than 50 years ago (Insel, 2010).

While schizophrenia is highly heritable, its etiology appears multifactorial. Twin and family studies have consistently demonstrated that schizophrenia has a strong genetic basis. The heritability is estimated about 60-80% (Sullivan, Kendler & Neale, 2003), and risk in siblings of affected individuals is 8-10 fold greater than for the general population. Several rare copy number variants (CNVs) identified only account for a small portion of schizophrenia cases, but they are also not specific for schizophrenia (International, 2008; Stefansson et al., 2008; Walsh et al., 2008). Associations with common genetic variants have not been consistently associated until a recent large genome-wide association study that identifies 108 independent susceptibility loci to schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics 2014). Several common variants have also been associated with schizophrenia in Han Chinese populations (Shi et al., 2011, Yue et al., 2011). Previously pathophysiological studies show that schizophrenia is a neurodevelopmental disorder

that involves alteration in brain circuit (Feinberg, 1982, Weinberger, 1987, Murray, Jones & O'Callaghan, 1991). Evidence from longitudinal study of magnetic resonance imaging also supports this neurodevelopment hypothesis (Paus, Keshavan & Giedd, 2008). Prenatal or perinatal environmental factors such as prenatal exposure to famine, infections in the second trimester, perinatal injury and cytokine exposure have been implicated for schizophrenia (Cannon, Jones & Murray, 2002; St Clair et al., 2005; Brown & Derkits, 2010; Ellman et al., 2010). Serious obstetric complications interact with hypoxia-regulated or vascular-expression genes to influence schizophrenia risk (Nicodemus et al., 2008).

While elucidating the etiology of schizophrenia is important for understanding the disease biology, identifying biological or psychological markers for early diagnosis will contribute to the development of effective preventive and treatment strategies. In the five-year plan, schizophrenia has been listed as one of the prioritized disease for research. Longitudinal study of schizophrenia high risk population will allow us to depict the trajectory of psychiatric disorders, and to decide when and how to conduct preventive intervention. On the other hand, study for evaluating the effectiveness or adverse effect of existing antipsychotic drugs should be conducted in a large-scale and in combination with other psychosocial intervention. Moreover, pharmacogenomics including study of drug clearance should also be conducted to assess how drug clearance affects effectiveness of therapeutic treatment. This may provide evidence to decide what treatment or intervention strategies should be developed into clinical practice.

Depression

Depression is a core trait in making diagnosis of mood disorders such as major depressive disorder, dysthymic disorder, bipolar disorder, and is an important clinical component of many psychiatric, neurological, and physical syndromes (American Psychiatric Association DSM-IV, 1994). Mood disorders are one of the leading causes of disability worldwide, with an estimated lifetime prevalence of 20% in the US population (Kessler et al., 2005). While it is not high as the Western society, the prevalence of depression in general populations of China is about 3.6 % in the metropolitan area (Lee et al., 2009), 12.3% in the migrant workers (Qiu et al., 2011) or even higher in college students (Peng et al., 2010). This may have implications for the intervention of mental health disorders in China. Over past three decades, the most dramatic change in the Chinese society is the urbanization or rural-urban migration. Many of migrants in particular migrant workers (i.e. men or women who leave for seeking work in the developed urban area temporarily, but remain their residential place in their hometown of the rural areas) may have to encounter difficulties in adapting to urban life, temporary poor housing, finding a job, and suffering from the separation from their families, which may cause excessive psychosocial stress. Studies have shown that the left-behind wife, children (He et al., 2012) and the elderly (He et al., 2015) have more tendency to develop depression (Lu, Hu & Treiman, 2012). While the modernization of China has created a lot of opportunities, the job market for college graduates has become competitive. This may cause a big psychosocial burden on the youth, especially senior college students who face an issue of employment. Depression is also more common in individuals who suffer from a variety of chronic conditions (Chen et al., 2005).

While depression is generally not a preventable condition, making change in lifestyle, providing psychological counseling or social supports or therapeutic treatment in time can play a role in its progression. China has a very low rate of the awareness of depression. A lot of people, or even general clinicians or doctors do not know what practical measures to be taken for depression. On the other hand, most people do not have accessibility to qualified

professionals, especially outside big cities. Increasing the awareness of depression and building mental health service centers to provide psychological counseling and social supports is critical for increasing the treatment rate of depression. This has been listed as prioritized area in the five-year mental health work plan.

Dementia

Dementia is a general term describing a range of symptoms associated with a decline in memory or other thinking abilities severe enough to affect individuals to perform daily activities. Among the multiple types of dementias such as Alzheimer's disease, Lewy body disease, Parkinson's disease with dementia, frontotemporal dementia, and vascular dementia, the dementia related to Alzheimer's disease (AD) and vascular dementia are most common forms. The proportion of subtype dementia is varied with geographic locations in China (Chiu & Zhang, 2000). People living in the northern areas tend to have a higher proportion of vascular dementia than the southern areas. The prevalence of dementia among the elderly aged 65 years is about 3-5%; and clinical diagnosed AD accounts for 65% of subjects with dementia (Zhang et al., 1990; Wang et al., 2000; Zhang et al., 2005). In 2010, the number of people with dementia was estimated at about 9.19 million (5.92-12.48) in China (Chan et al., 2013); and this number will increase greatly as the rapid population aging.

Dementia has become an emerging health burden in China. Due to the implementation of family planning policy over more than three decades, China has witnessed a faster demographic transition from high birth and death rates to low birth and death rates, which are normally driven by economic development in the industrialized countries (Huang, Yu & Koplan, 2014). In the urban areas, the 4-2-1 or 4-2-2 family structure is the predominant form, i.e. a typical family with 4 elderly, 1 couple and 1 or 2 children. This will be a huge challenge to the traditional elderly care system that the elderly used to be taken care of by their children (Chu & Chi, 2008). By the 2030, China will be the most aged society in the world, with the more than 200 millions of people aged 65 years or older (Feng, Liu, Guan & Mor, 2012). The rapid aging not in proportional to its income per capita will bring a big burden for the society in the care for the elderly.

The care for patients with dementia is an emerging issue. Despite intensive research efforts, only cholinesterase inhibitors and memantine are approved to treat mild to moderate dementias (Riordan et al., 2011). Current treatments have only marginal benefits on symptoms, and there are no effective preventive interventions and no medication that can cure dementia (Chouraki & Seshadri, 2014). Delusions, hallucinations, aggression, and agitation affect more than half of patients with Alzheimer's disease and related dementias. Evidence has shown that antipsychotic treatment using atypical antipsychotic drugs (olanzapine, quetiapine and risperidone) offers little advantage in comparison with placebo due to adverse effects (Schneider, Tariot et al. 2006). Individuals with dementia tend to have symptoms of depression and other behavioral and psychological symptoms of dementia (BPSD), which may require more care and therapeutic needs (Chen et al., 2014). In China, patients with dementia are mostly taken care at home by their children and spouse. Studies have indicated that long-term relative caregivers for dementia tend to have an increase rate of depression (Watson, Lewis, Moore & Jeste, 2011). The care burden and psychological health of dementia caregivers are also a major health problem. Building infrastructure and service network through long-term care or nursing home will help to reduce family burden of the dementia care.

Study of identifying genetic and environment risk factors can provide evidence for effective early detection and intervention of dementia. Genetic studies of Alzheimer's disease appear to be more consistent compared with other neuropsychiatric disorders.

Mutations in three genes (i.e. Amyloid Precursor Protein, APP; presenilin 1, PSEN1; presenilin 2, PSEN2) account for 50% of all familial forms of AD (Nacmias et al., 2014), which tends to develop before age of 65 years (early onset of AD). However, majority of AD cases are late onset (LOAD). While no obvious pattern of inheritance, Apolipoprotein E is consistently associated with risk of LOAD, and accounts for 3.7% of variation in age of onset, which is higher than all other loci together (Naj et al., 2014). A large body of evidences show that the ApoE4 allele alone, or interacting with other genetic variants or with environmental factors such as stressful life events, contributes to the elevated risk of LOAD, cardiovascular diseases (Raichlen & Alexander, 2014), aging and exceptional longevity (Garatachea et al., 2015), cognitive decline, and self-reported health among older adults (Zhang et al., 2008, Zeng et al., 2011). While with some ethical and practice concerns or in debate, genetic testing for gene like ApoE4 among older adults may help to make early diagnosis and to develop effective intervention strategies for dementia (Sun et al., 2012). Development of new treatment and intervention, improving the effective use of existing drugs or exploring alternative medicine such as traditional Chinese medicine, may help to reduce the economic cost of treatment for dementia (Kalaria et al., 2008).

Implications for Neuropsychiatric Medicine

The disease areas of the focus in the China's five-year mental health work plan have important implications for neuropsychiatric medicine. Autism is relatively new in terms of public awareness, clinical diagnosis and therapeutic treatment. While it is believed as a neurodevelopmental disorder, its etiology has yet to be clear. Schizophrenia is more severe mental health disorder; both clinical and basic research has been particularly emphasized in the plan. The development of preventive strategies based on scientific research will be critical for schizophrenia, especially for early detection and intervention. Depression is a common and core trait for multiple psychiatric and neurological disorders, and predominantly develops in adults who suffer from excessive psychosocial stress; whereas dementia is a severe common disorder for the elderly, probably as a result of the interaction between gene and lifetime environment such as lifestyle. Depression and cognitive impairment are two core traits for neuropsychiatric disorders. Study of these disorders may contribute to a better understanding of the etiology and biology of other neuropsychiatric disorders such as schizophrenia.

Clinical and translational research on a large cohort study of mental health disorders with modern technology of genomics, systems biology and neuroscience, or experimental medicine will accelerate biomedical discovery and translate new tools into more effective strategies in treatment and prevention of these disorders. This would be in line with the recent announced precision medicine initiative that develops treatment and intervention strategies that take individual variability into account (Collins & Varmus, 2015). With advances in genomics technology, pharmacogenomics appears to be promising in identifying genetic variants associated with response to existing therapeutic treatment such as atypical antipsychotic drugs. This would allow to develop genotype-guide therapy for neuropsychiatric diseases (Apud et al., 2012). Because of the centralized health care and hospital-based medical service system, China has the unique advantage in utilizing clinical resources for translational research. More effort to research activities on mental health disorders should be increased in order to develop effective therapeutic treatment or intervention on the mental health disorders effectively.

In addition to biological psychiatry, social aspects of mental disorders have been emphasized in the goals of mental health work plan. Social stigma of mental illness is another issue for mental health care and may have negative on self-esteem and self-efficacy

which may affect the compliance of psychosocial treatment. In east Asian countries like China, the local terms for dementia are derogatory. Individuals with dementia and their family members may carry a social stigma that prevents them from seeking for diagnosis and treatment. Change in the local terms of dementia has become attention in the scientific community (Chiu et al., 2014). Psychosocial counseling and social support may have impact on mental illness. Social support is one of social factors affecting the recovery process of patients with mental health disorders, but could be also a source of stigma (Podogrodzka-Niell & Tyszkowska, 2014). The China mental health law provide a protection guideline for patients with mental disorders and their families, and it can be a safeguard to patients' privacy, and stresses that requirement of voluntary treatment for patients with mental disorders. Meanwhile, study has shown that selective disclosure can optimize social support and limited stigmatization (Bos et al., 2009). To fight against the mental health disorders, intervention and treatment designed to reduce social stigma should also be of consideration. This is especially important for mental health care in China.

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