

Required Research Activities to Overcome Addiction Problems in Japan

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Abstract

Background: The term “addiction” encompasses both substance dependence and behavioral addiction and is associated with major societal problems. Measures to combat addiction are currently insufficient in Japan, and further research on addiction is necessary. **Methods:** Science Council of Japan (SCJ) has three subcommittees – the Addiction Subcommittee, Brain and Mind Subcommittee, and Neuroscience Subcommittee among others. Those three subcommittees are dealing directly or indirectly with addiction problems in Japan. Thus, all authors of this review, members of those subcommittees, collectively recommended what research activities are required in Japan for continuing effort in overcoming addiction problems in Japan. **Results:** We proposed the following measures. Proposal 1: Understand diversity in addiction and promote related research and education; Proposal 2: Promote personalized measures for patients with addiction disorders; Proposal 3: Foster addiction research personnel; Proposal 4: Develop new guidelines for the rehabilitation of patients with drug dependence; Proposal 5: Establish an institute specializing in addiction research and comprehensively handling information collection, research, countermeasures, treatment, and public relation related to addiction. **Conclusion:** The opinions of the review are based on the recommendations that were published in 2020 in Japanese by the Addiction Subcommittee, Brain and Mind Subcommittee, and Neuroscience Subcommittee of the SCJ. The authors here are sharing colleagues of *Taiwanese Society of Psychiatry* with these proposed research activities required to overcome addiction problems in Japan.

Key words: behavioral addiction, drug dependence, information sharing, personalized medicine
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Introduction

Addiction includes both substance dependence (e.g., alcohol dependence, methamphetamine dependence, and opioid dependence) and behavioral addiction (e.g., gambling disorder and gaming disorder). Addiction affects both the mind and body of the person and social activities and continues to be a major

social problem. The *Diet*, the national legislature of Japan, and media have also stated the need for further addiction research and countermeasures, but practical measures have not yet been implemented in Japan. The number of patients with addiction

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disorders is estimated to be 100,000 for drug dependence, 800,000 for alcohol dependence, 18 million for nicotine dependence, and 3.2 million for gambling disorders in Japan. In addition, the number of adults with Internet addiction is estimated to be 4.2 million. These surveys of the prevalence of addiction may be insufficient because many people have difficulty honestly self-reporting their addiction status because of the stigma against people with addiction in Japan. Such stigma hampers medical treatment and social measures against addiction. Furthermore, addiction disorders are frequently comorbid with various psychiatric disorders, particularly depression. The high rate of comorbidity contributes to the tremendously high time and cost that are needed for addiction treatment. Although medications are available for some addiction disorders, none are available for most of them. As the result, most patients struggle with their addiction alone or depend on care from family members or self-help groups. The reasons why measures against addiction disorders have not appreciably progressed in Japan are many, including a lack of social understanding that addiction disorders are indeed disorders, the insufficiency of epidemiological investigations of addiction, the lack of understanding the etiology of addiction disorders, the difficulty developing therapeutic agents and treatment methods that directly target the etiology of addiction, the complex nature of the pathophysiology of addiction disorders, and mostly heterogeneous patient groups that are evaluated in clinical studies of addiction.

Science Council of Japan

Similar to the National Academy of Sciences in the United States of America, Japan has Science Council of Japan (SCJ), the representative organization of Japanese scientist community ranging over all fields of sciences subsuming humanities, social sciences, life sciences, natural sciences, and engineering (www.scj.go.jp/en/). SCJ was established in January 1949 as a “special organization” under the jurisdiction of the Prime Minister, operating independently of the government, for the purpose of promoting and enhancing the field of science and having science reflected in and permeated into administration, industries, and people’s lives. It represents Japan’s scientists both domestically and internationally with the firm belief that science is the foundation upon which a civilized nation is built.

SCJ has two functions:

- To deliberate on important issues concerning science and help solve such issues
- To make coordination among scientific studies to achieve higher efficiency.

With a focus on the following four activities, SCJ is extremely active in its deliberations, helping improve and develop science in Japan and strengthening the inseparable alliance with the Council for Science and Technology Policy, which is the command center for Japan’s science and technology policies.

- Policy recommendations to the government and public
- International activities
- Promotion of scientific literacy

- Establishment of networks among scientists.

SCJ consists of 210 council members and some 2,000 members. SCJ organization comprises the General Assembly, three Section Meetings, the Executive Board, 30 Specialty Committees, four Administrative Committees for Operation, and Issue-centered *ad hoc* Committees.

Problems Related to Addiction and the Status of Countermeasures in Japan

In Japan, narcotics and stimulants have long been controlled under legal regulations. The Basic Law on Measures to Prevent Damage to Health due to Alcohol was enacted in May 2014. In addition to the treatment of health problems among patients with alcoholism, the prevention of alcohol-related problems, such as fetal alcohol spectrum disorders and domestic violence, has received growing attention, with actions taken by national and local governments. Pachinko is a game that is quite popular among the public in Japan, in addition to horse races, bicycle races, and motor boat races. Lotteries are also quite popular. Furthermore, casino facilities have been addressed by the government and the Act on Promotion of Development of Specified Integrated Resort Districts and Basic Law on Measures against Gambling Addiction, which were enacted in July 2018 and October 2018, respectively. The World Health Organization lists gambling disorders in the *International Statistical Classification of Diseases and Related Health Problems, 11th edition (ICD-11)* [1], and the range of substances and behaviors that should be treated as addiction disorders is expanding. A research group in the Ministry of Health, Labour and Welfare in Japan reported that the ratio of pathological gamblers in Japan was higher than in other countries, based on their investigations in 2013 and 2017 [2]. The estimated annual social loss, including medical expenses, labor/employment loss, and public measure costs that are attributable to substance dependence, is currently more than 8.5 trillion Japanese yen. Social loss that is caused by behavioral addiction, such as gambling, has not been precisely estimated but is considered to be expanding. However, no information is available about the additive or synergistic risks of substance dependence and behavioral addiction, thus hampering the development and implementation of effective measures.

The rate of lifetime illegal drug use is 2.4% among the national population in Japan, whereas this rate in other major countries is 25%–42% [3, 4]. In Japan, the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act) in 2017 banned the importation, manufacture, possession, and use of PMD Act Designated Substances that have a high probability of having psychotoxicity (hallucination and excitement/suppression of the central nervous system) and may cause health hazards when used by humans. The use of PMD Act Designated Substances other than approved chemical syntheses is prohibited. In addition, comprehensive designation that regulates all compounds with different functional groups began

in 2013 to stop the never-ending repetition of novel addictive substance use and its regulation. Synthetic cannabinoids and cathinones are comprehensively designated. These regulations as primary preventive measures successfully minimize problems of designer drugs. Strong primary preventive measures increase stigma for users of addictive substances and make secondary preventive measures (e.g., early detection and early treatment) and tertiary preventive measures (e.g., social rehabilitation) difficult. The number of medical institutions did not increase, even after enforcement of the “Partial Suspension of Execution of Sentence.” Based on recent scientific findings that drug dependence is a brain disorder, the further promotion of secondary and tertiary preventive measures against drug dependences is required. In addition to illegal drugs, prescription medications, such as anxiolytics and hypnotics, are also associated with a high risk of dependence. Physical dependence that is caused by even prescribed amounts of these medications is known to be problematic. Investigations of prescription drug dependence have not yet been sufficiently conducted, and most medical doctors in Japan do not recognize this problem.

The sensitivity to various substances is ethnically and individually different. The research findings in populations in Western countries cannot always be applicable to Asian populations. With regard to behavioral addiction, specific problems and appropriate countermeasures also differ among countries because the type and penetration of various media and devices and social environments are significantly different. Therefore, domestic problems of addiction need to be tackled on the national level, and research and countermeasures need to be conducted independently, all while simultaneously collecting information on specific problems and countermeasures in other countries. The current situation of behavioral addiction has not been well investigated in Japan. To accurately grasp individual states of addiction, asking simple questions about personal experiences is insufficient. Systematic and standardized scales are useful. It is also important to enlighten people about the fact that addiction disorders are brain disorders and may be treatable if details about abnormal brain function are identified.

A report from a research group in the Ministry of Health, Labour and Welfare in Japan showed that the number of adult patients with internet disorders, including smartphone disorders, increased 1.5 fold from 2008 to 2013 and reached 4.2 million people [5]. The problems include not only addiction disorders themselves but also poor mental health and academic performance in adolescents, societal withdrawal of adults, distress and debt that are caused by gambling, and the abandonment of childcare. Mental health problems that are caused by excess internet use are complicated because the internet provides an escape from the world among patients with various mental illnesses (e.g., depression, developmental disorders, and anxiety disorders, among others) and a useful means for connecting them with society. In addition, it is difficult to completely avoid the internet because it is commonly a daily necessity for both social and work life. It is

socially urgent to reveal the pathogenesis of internet disorders and gaming disorders and develop effective treatments.

The development of therapeutic agents is indispensable for the pharmacotherapy of addiction disorders, and continued research and development are underway worldwide. To date, pharmacotherapies are available for the treatment of some addictive substances (Table 1). With regard to substance dependence, several medications are available for dependence on opioids, alcohol, and nicotine but not for dependence on stimulants, including methamphetamine and cocaine. With regard to behavioral addiction, no medications or pharmacotherapies are under development, and only one is in the research stage. In Japan, only medications for alcohol and nicotine dependence are available, with no medications for drug dependence or behavioral addictions. Importantly, no candidate compounds have been proposed for behavioral addiction, even in the development stage.

Addiction disorders are mainly treated by psychosocial therapy, such as cognitive behavioral therapy. Approved medications specifically for addiction are limited in Japan (Table 2). Drug dependence tends to be seen as an extension of crime, and patients with drug dependence are often treated as criminals rather than as suffering patients. Therefore, patients with drug dependence usually undergo withdrawal and rehabilitation rather than medical treatment. Drug dependence is classified as a treatable disorder in many countries, and it should be medically treated like alcoholism and nicotine addiction. Although gambling disorder is classified in the same category as substance use disorders in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)* [6], and although gaming disorder is classified as a disorder in the *ICD-11*, treatments for these disorders have not been established, and medical fee items are not sufficient in Japan (Table 2). There are no insurance disease names for behavioral addiction disorders in Japan. Thus, these disorders should be treated as a different insurance disease. In addition, addiction group therapy as a medical fee item cannot be paid when personal psychotherapy is concurrently given to patients in Japan. In addition to medical programs, the development of educational programs is needed for addiction problems, especially when considering that addictive substances are used by adolescents, and the starting age of Internet use and gaming has become lower.

Five Proposals for Addiction Research in Japan

Proposal 1. Understand diversity in addiction and promote related research and education

Social issues about addiction are different in different countries. Research on substance dependence is performed independently, and it is not always integrated. Behavioral addiction disorders have expanded and are diverse, but the current state of behavioral addiction in Japan has not been well investigated. Common bases of substance dependence and behavioral addiction and their differences

have not yet been fully grasped. In Japan, such research and countermeasures have not been efficiently integrated. A comprehensive system is needed for the prevention, treatment, research, and education of addiction that accurately reflects the current state of addiction among the Japanese population and can flexibly respond to the current and future states of addiction.

Proposal 2. Promote personalized measures for patients with addiction disorders

Vulnerability to addiction disorders is individually different because of environmental factors and genetic factors. Large

individual differences in vulnerability hamper efficient prevention and treatment. Research on human genetics has recently made great progress, and genetic factors that underlie individual differences in the sensitivity to addictive substances are being revealed (Table 3) [7]. Such findings hold promise for personalized prevention and treatment strategies for addiction disorders. We propose comprehensive studies that focus on genetic factors of individual differences in the vulnerability to addiction disorders and the development of addiction disorders in patients and the establishment of a system that can provide personalized medicine for addiction treatment (Figure 1).

Table 1. Launch and development status of drugs for the treatment of various addiction disorders (Japan/world)

| Target | Launched | Approval | Phase 3 | Phase 2 | Phase 1 | Study stage |
|----------|----------|----------|---------|---------|---------|-------------|
| Drug | 0/6 | 0/1 | 0/3 | 0/9 | 0/12 | 74 |
| Alcohol | 4/5 | 0/1 | 0/3 | 0/12 | 0/5 | 14 |
| Nicotine | 2/3 | 0/2 | 0/2 | 0/9 | 0/6 | 25 |
| Gambling | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1 |

Data sources: Clarivate: Cortellis Competitive Intelligence. Philadelphia, USA (www.cortellis.com/intelligence/login.do), surveyed on February 6, 2019; and Technomics, Inc.: Asu-no-shinyaku. Tokyo, Japan (<https://asushin2.com/>), surveyed on July 10, 2019. The study stage shows the number worldwide. For products that are already on the market, the active substance of the drug is counted, and multiple products that are on the market are not separately counted because of differences in the preparation of the same active substance

Table 2. Current status of addiction treatment in Japan

| Target | Medication | Medical fee items |
|--|---|--|
| Abused drugs | None | Addiction group therapy |
| Alcohol | Acamprosate Nalmefene Disulfiram Cyanamide | Severe alcoholism, inpatient medical management |
| Nicotine | Varenicline, Nicotine replacement therapy | Nicotine Addiction Management Fee |
| Behavioral addiction | None | Addiction group therapy |
| Psychiatric specialty therapy not specialized in addiction | | Outpatient psychotherapy, outpatient group therapy, day care, psychiatric night care, psychiatric short care, psychiatric occupational therapy |

Table 3. Major polymorphisms reported by meta-analyses to be associated with substance dependence

| Related genes (regions) | Polymorphisms reported to be related, etc. | Target substance | References |
|-----------------------------|--|--------------------|---|
| <i>TTC12/ANKK1/DRD2</i> | rs1800497 (Taq1A) | Alcohol | Munafò et al. <i>Mol Psychiatry</i> (2007) [8] |
| <i>SLC6A4</i> | 5-HTTLPR | Alcohol | McHugh et al. <i>Drug Alcohol Depend</i> (2010) [9] |
| <i>TNF</i> | rs361525 (-238 G/A) | Alcohol | Kebir et al. <i>Eur Addict Res</i> (2011) [10] |
| <i>ADH1B</i> | rs1229984 (Arg48His) | Alcohol | Li et al. <i>Biol Psychiatry</i> (2011) [11] |
| <i>ALDH2</i> | rs671 (Glu504Lys) | Alcohol | Li et al. <i>Hum Genet</i> (2012) [12] |
| <i>ADH1C</i> | rs698 (Ile350Val) | Alcohol | Li et al. <i>Hum Genet</i> (2012) [13] |
| <i>TPH 1</i> | rs1800532 (A218C) | Alcohol | Chen et al. <i>J Affect Disord</i> (2012) [14] |
| <i>CHRNA5/CHRNA3/CHRNA4</i> | rs16969968 | Nicotine | Olfson et al. <i>Mol Psychiatry</i> (2016) [15] |
| <i>CYP2A6</i> | Reduced-activity polymorphisms | Nicotine | Munafò et al. <i>Nicotine Tob Res</i> (2004) [16] |
| <i>DAT1</i> | 3'-UTR VNTR | Nicotine | Stapleton et al. <i>Addict Biol</i> (2007) [17] |
| <i>TTC12/ANKK1/DRD2</i> | rs1800497 (Taq1A) | Nicotine | Ma et al. <i>Transl Psychiatry</i> (2015) [18] |
| <i>SLC6A4</i> | 5-HTTLPR | Nicotine | Munafò et al. <i>Nicotine Tob Res</i> (2004) [16] |
| <i>SLC6A4</i> | 5-HTTLPR | Stimulants/cocaine | Cao et al. <i>Neuropsychopharmacology</i> (2013) [19] |
| <i>BDNF</i> | rs6265 | Stimulants | Haerian <i>Pharmacogenomics</i> (2013) [20] |
| <i>CNRI</i> | rs6454674 | Cocaine | Clarke et al. <i>Addict Biol</i> (2013) [21] |
| <i>OPRD1</i> | rs678849 | Cocaine | Crist et al. <i>Drug Alcohol Depend</i> (2013) [22] |

Source: *Addiction Science* [7]. Excerpt from Table 8.1 of “8. Molecular biological basics of drug sensitivity”

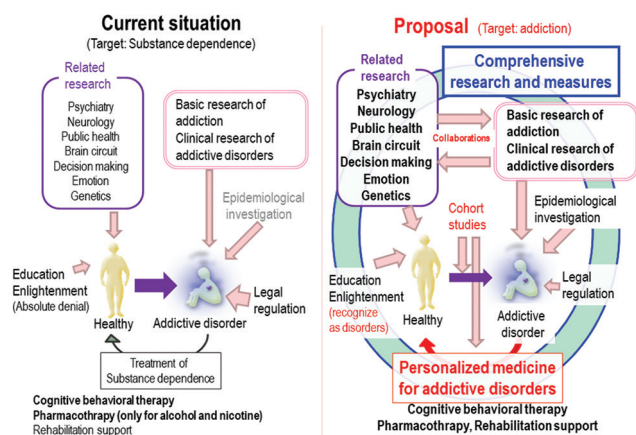


Figure 1. Conceptual diagram of a personalized medical system for addiction disorders.

Proposal 3. Foster addiction research personnel

The number of addiction researchers has been decreasing, partly because of an insufficient research system for addiction and a remarkably small number of grants for addiction research in Japan compared with other countries. We propose the establishment of a research system that is based on public-private partnerships and more research grants for addiction. Addiction research is in an interdisciplinary area that is related to various academic fields, including psychiatry, psychology, pharmacology, neuroscience, forensic medicine, pedagogy, and law. Researchers in related fields should participate and collaborate in addiction research, and such collaborative research should be supported.

Proposal 4. Develop new guidelines for the rehabilitation of patients with drug dependence

The rate of lifetime drug use among the Japanese population has been successfully kept extremely low because of a strict punishment policy for drug problems relative to other countries. However, such strict punishment can also alienate patients with drug dependence and hinder their treatment and recovery. Over recent years, the United Nations has issued a series of statements on the harmful effects of strict punishment policies for drug problems. Similar to other countries, Japan should shift its focus from strict punishment policies to measures that consider the development of treatment systems and methods and reducing secondary damage that is caused by addictive substance use. To guarantee a treatment environment where people who suffer from drug dependence can receive adequate treatment and peace of mind and create a social environment where patients with drug dependence are not isolated and can more easily recover, we propose the development of new guidelines to rehabilitate patients with drug dependence.

Proposal 5. Establish an institute that specializes in addiction research and comprehensively handles information collection, research, countermeasures, treatment, and public relations related to addiction

In Japan, addiction research is mainly conducted within individual research units. In other countries, such research

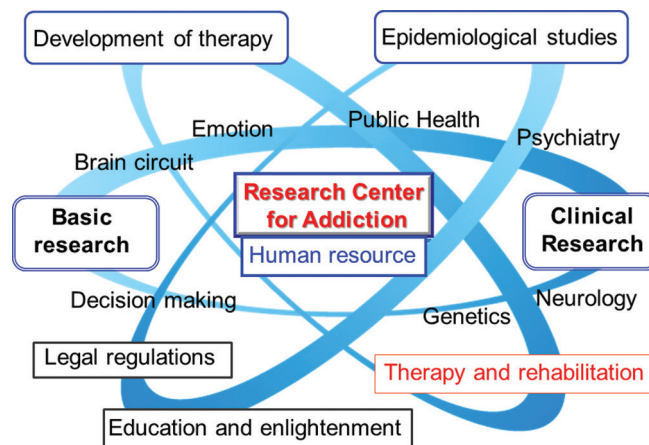


Figure 2. Conceptual diagram of a comprehensive addiction research system.

is conducted under the auspices and leadership of dedicated institutes that specialize in addiction research. It is difficult to conduct systematic research on addiction because of differences in research designs between institutions and the lack of research grant support. Based on Proposals 1–4, we propose the establishment of a Japanese center for addiction research that comprehensively addresses various kinds of addiction, including substance dependence and behavioral addiction, to further our understanding of addiction disorders and establish appropriate prevention, treatment, and rehabilitation strategies (Figure 2).

Conclusion

The authors here are sharing colleagues of *Taiwanese Society of Psychiatry* with this our proposed required research activities to overcome addiction problems in Japan. We welcome any comments from Taiwanese colleagues.

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Conflicts of Interest

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