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GUIDELINES

Guideline for pharmacological treatment of schizophrenia 2022

Japanese Society of Neuropsychopharmacology | Japanese Society of Clinical Neuropsychopharmacology

Correspondence
Japanese Society of Neuropsychopharmacology
Email: jsnp@aeplan.co.jp

Japanese Society of Clinical Neuropsychopharmacology
Email: jscnp@aeplan.co.jp

ENGLISH TRANSLATION TEAM (AFFILIATION AS OF JUNE 2024)

Hiroyoshi Takeuchi, MD, PhD, Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

Kayo Ichihashi, MD, PhD, Department of Neuropsychiatry, University of Tokyo Hospital, Tokyo, Japan

Junichi Iga, MD, PhD, Department of Neuropsychiatry, Ehime University Graduate School of Medicine, Toon, Japan

Taro Kishi, MD, PhD, Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Japan

Itaru Miura, MD, PhD, Department of Neuropsychiatry, Fukushima Medical University School of Medicine, Fukushima, Japan

Kenji Sakuma, MD, PhD, Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Japan

Tsuyoshi Sasaki, MD, PhD, Department of Child Psychiatry and Psychiatry, Chiba University Hospital, Chiba, Japan

Hideki Sato, MD, MA, PhD, Department of Psychiatry, National Center Hospital, National Center of Neurology and Psychiatry, Kodaira, Japan

Yoshiteru Takekita, MD, PhD, Department of Neuropsychiatry, Faculty of Medicine, Kansai Medical University, Hirakata, Japan

Seiichiro Tarutani, MD, PhD, Department of Psychiatry, Shin-Abuyama Hospital, Osaka Institute of Clinical Psychiatry, Takatsuki, Japan

Tetsu Tomita, MD, PhD, Department of Neuropsychiatry, Graduate School of Medicine, Hirosaki University, Hirosaki, Japan

Tetsufumi Kanazawa, MD, PhD, Department of Neuropsychiatry Osaka Medical and Pharmaceutical University, Takatsuki, Japan

Saya Kikuchi, MD, PhD, Department of Psychiatry, Graduate School of Medicine, Tohoku University, Sendai, Japan

Hiroshi Kimura, MD, PhD, Department of Psychiatry, Gakuji-kai Kimura Hospital, Chiba, Japan/Department of Psychiatry, International University of Health and Welfare (IUHW), Narita, Japan

Shusuke Numata, MD, PhD, Department of Psychiatry, Graduate School of Biomedical Science, Tokushima University, Tokushima, Japan

Shinichiro Ochi, MD, PhD, Department of Neuropsychiatry, Ehime University Graduate School of Medicine, Toon, Japan

Kiyotaka Nemoto, MD, PhD, Department of Psychiatry, Institute of Medicine, University of Tsukuba, Tsukuba, Japan

Kazuto Oya, MD, PhD, Jindai Hospital, Toyota, Japan

Norio Yasui-Furukori, MD, PhD, Department of Psychiatry, Dokkyo Medical University School of Medicine, Shimotsuga, Japan

Ryota Hashimoto, MD, PhD, Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Japan

Ken Inada, MD, PhD, Department of Psychiatry, Kitasato University School of Medicine, Sagamihara, Japan

ENGLISH TRANSLATION TEAM (COI AS OF 2021–2023)

Hiroyoshi Takeuchi has received grants from Daiichi Sankyo, Novartis Pharma, and Otsuka; speaker fees from EA Pharma, Eisai, Janssen, Kyowa, Lundbeck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, MSD, Otsuka, Sumitomo Pharma, Takeda, and Yoshitomiyakuhin;

and consulting fees from Boehringer Ingelheim, Janssen, Mitsubishi Tanabe Pharma, Ono, and Sumitomo Pharma.

Kayo Ichihashi received honoraria for educational events from Janssen Pharmaceutical K.K., for lectures from MSD Co. Ltd., Nobelpharma Co. Ltd., and Takeda Pharmaceutical Co. Ltd.

Jun-ichi Iga received personal fees from Otsuka, Takeda, Daiichi Sankyo, Eisai, Janssen, Lundbeck Japan, Meiji Seika Pharma, Mochida, MSD, Shionogi, Sumitomo Pharma, Yoshitomiyakuhin, Viatris, Sanofi, Boehringer Ingelheim, Kyowa, Kowa, Nobelpharma, and Yonyaku in the last 3 years.

Taro Kishi has received speaker's honoraria from Eisai, Janssen, Meiji, Otsuka, Sumitomo, Takeda, Mitsubishi Tanabe, Kyowa, Yoshitomi, and Viatris and research grants from Eisai, JSPS KAKENHI (19 K08082 and 23 K06998), Japan Agency for Medical Research and Development (JP22dk0307107 and JP22wm0525024), and the Japanese Ministry of Health, Labour and Welfare (21GC1018).

Itaru Miura has received speaker's honoraria from Eisai, Janssen, Meiji Seika Pharma, MSD, Otsuka, Sumitomo, Takeda, Tanabe Mitsubishi, Towa, Yoshitomi, and Viatris.

Kenji Sakuma has received speaker's honoraria from Daiichi Sankyo, Janssen, Lundbeck, Meiji, Otsuka, Sumitomo, and Takeda and has received Grant-in-Aid for Young Scientists (B) (19K17099), Grant-in-Aid for Scientific Research (C) (23K06998), and Japan Agency for Medical Research and Development (JP22dk0307107 and JP23dk0307122).

Tsuyoshi Sasaki has received honoraria for lectures from Eisai, Janssen, Meiji Seika Pharma, Mochida, Nobel Pharma, Otsuka, Shionogi, Sumitomo Pharma, Takeda, Viatris, Yoshitomi, and Yui Connection within the last 3 years. The organization to which Tsuyoshi Sasaki belongs has also received research grant support for the organization from Eisai, Otsuka, Shionogi, Sumitomo Pharma, Takeda, Tanabe Mitsubishi, and Viatris in the organization to which Tsuyoshi Sasaki belongs within the last 3 years.

Hideki Sato received research grants from Nippon Boehringer Ingelheim Co. Ltd., Lundbeck Japan K.K., Biogen Japan Ltd., Mitsubishi Tanabe Pharma Corporation, and Novartis Pharma K.K.

Yoshiteru Takekita has received grant funding from the Japan Society for the Promotion of Science and speaker's honoraria from Meiji Seika Pharma, Sumitomo Pharma, Janssen Pharmaceutical, Otsuka, Eisai, MSD K.K. Daiichi Sankyo, Pfizer, UCB Japan, and Takeda Pharmaceutical.

Seiichiro Tarutani has received consulting fees from Janssen Pharmaceutical K.K. and honoraria for lectures from Otsuka Pharmaceutical Co. Ltd., Sumitomo Pharma Co. Ltd., Mochida Pharmaceutical Co. Ltd., Shionogi Pharma Co. Ltd., Viatris Inc., Janssen Pharmaceutical K.K., and Yoshitomiyakuhin Co.

Tetsu Tomita has received honoraria lecture fees from Meiji Seika Pharma Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co. Ltd., Yoshitomiyakuhin Co., Sumitomo Pharma Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Eisai Co. Ltd., MSD K.K., Viatris Inc., and Janssen Pharmaceutical K.K.

Tetsufumi Kanazawa has received speaker's honoraria from EA Pharma, Meiji Seika Pharma, MSD, Viatoris Japan, Eisai, Otsuka Pharmaceutical, Kowa, Sumitomo Pharma, Daiichi Sankyo, Takeda, Nippon Boehringer Ingelheim, Lundbeck Japan, Kyowa Pharmaceutical, Yoshitomi Pharmaceutical, and research grants from Otsuka Pharmaceutical Company, Sumitomo Pharma.

Hiroshi Kimura has received speaker's honoraria from Janssen Pharmaceutical K.K., Meiji Seika Pharma Co. Ltd., MSD K.K., Otsuka Pharmaceutical Co. Ltd., Sumitomo Pharma Co. Ltd., Takeda Pharmaceutical Co. Ltd., and Teijin Pharma Co. Ltd.

Saya Kikuchi has received honoraria for lectures from Sumitomo Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Yoshitomiyakuhin Co., Takeda Pharmaceutical Co., Ltd., Kyowa Pharmaceutical Industry Co., Ltd., Meiji Seika Pharma Co., Ltd., Viatris Inc., and MSD K.K.

Kiyotaka Nemoto has received honoraria for lectures from Eisai, Eli Lilly, Janssen, Lundbeck Japan, Meiji Seika Pharma, Mochida, MSD, Otsuka, Sumitomo Pharma, Yoshitomiyakuhin, and Viatris in the last 3 years.

Shusuke Numata has received rewards for lectures from Sumitomo Pharma Co., Ltd., MSD K.K., Lundbeck Japan K.K., Meiji Seika Pharma Co., Ltd., TEIJIN PHARMA LIMITED., Mitsubishi Tanabe Pharma Corporation., DAIICHI SANKYO COMPANY, LIMITED., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited., Janssen Pharmaceutical K.K., Mochida Pharmaceutical Co. Ltd., Kowa Co., Ltd., Yoshitomiyakuhin Corporation and research grants from Otsuka Pharmaceutical Co. Ltd., Sumitomo Pharma Co., Ltd.

Shinichiro Ochi received rewards for lectures from Sumitomo Pharma Co. Ltd., Meiji Seika Pharma Co. Ltd., Otsuka Pharmaceutical Co. Ltd., and Eisai Co., Ltd.

Kazuto Oya has received honoraria for lectures from EA Pharma Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Kyowa Pharmaceutical Industry Co., Ltd., Meiji Seika Pharma Co., Otsuka Pharmaceutical Co., Ltd., Sumitomo Pharma Co., Ltd., UCB Japan Co. Ltd., Viatris Inc., and Yoshitomiyakuhin Co., Ltd.

Norio Yasui-Furukori has received honoraria for lectures from Eisai, Eli Lilly, Janssen, Lundbeck Japan, Meiji Seika Pharma, Mochida, MSD, Otsuka, Sumitomo Pharma, Yoshitomiyakuhin, Viatris, EA Pharma, and Tsumura in the last 3 years.

Ryota Hashimoto received honoraria for lectures from Otsuka Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Sumitomo Pharma Co., Ltd., and Meiji Seika Pharma Co., Ltd., and received honoraria for scientific interview from Boehringer Ingelheim International GmbH.

Ken Inada received personal fees from Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Lundbeck Japan, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, Mochida, MSD, Nipro, Novartis, Otsuka, Pfizer, Shionogi, Sumitomo Pharma, Yoshitomiyakuhin, and Viatris, and he received research grant support from Mochida, Otsuka and Sumitomo pharma in the last 3 years.

INTRODUCTION

History of the creation of the Guideline for Pharmacological Treatment of Schizophrenia

In 2015, the Japanese Society of Neuropsychopharmacology created and published the "Guideline for Pharmacological Treatment of Schizophrenia." Since 2016, we have been holding seminars on these guidelines for medical professionals; and in 2018, we published a guideline book for the general public titled "Guide for Pharmacological Therapy of Schizophrenia: For Patients, Families, and Supporters" and worked to disseminate it. We have obtained many opinions through these books and seminars, and new evidence was acquired through continued research, which has necessitated the renewal of existing information. Therefore, in 2018, the Japanese Society of Neuropsychopharmacology and the Japanese Society of Clinical Neuropsychopharmacology began working to revise the guideline.

In the revised edition, we not only updated the information based on new evidence but also made the following changes:

First, various stakeholders, such as the patients, families, supporters, and related organizations, became committee members and worked together to prepare a report. Clinical questions (CQs) and outcomes were added not only from the perspective of the psychiatrist but also from the perspective of the patient, family, and supporter. The contents of this guideline also adopted the unanimous principles.

(Note: The term "patients" means as "patients," "affected individuals," "stake holders," "health care users," all terms are unified as "patients" in this guideline.)

Second, treatment of schizophrenia should be comprehensive, including psychosocial treatment combined with psychiatric welfare services, rather than pharmacological treatment alone. Thus, we have clearly stated this point in Part 1 "Formulation of schizophrenia therapy plan" and separated CQs into Part 2.

Individuals responsible for composing the "Guideline for Pharmacological Treatment of Schizophrenia"

The roles of the task force members were in accordance with the methods of the Japan Council for Quality Health Care EBM and Guideline-Promoting Project (Minds).

Co-representatives

Kazuyuki Nakagome	National Center of Neurology and Psychiatry
Toshiyuki Someya	Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences

Committee members

Hitoshi Iida	Department of Psychiatry, Faculty of Medicine, Fukuoka University
Junichi Iga	Department Neuropsychiatry, Ehime University Graduate School of Medicine
Ataru Igarashi	Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine
Shunichiro Ikeda	Department of Neuropsychiatry, Kansai Medical University
Kayo Ichihashi	Department of Neuropsychiatry, University of Tokyo Hospital
Masanobu Ito	Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine
Koki Ito	Sapporo City General Hospital Psychiatry Clinic / Psychiatric Medical Center
Ataru Inagaki	College of Education, Psychology and Human Studies / Health Administration Center, Aoyama Gakuin University
Ken Inada	Department of Psychiatry, School of Medicine, Kitasato University
Masaomi Iyo	Department of Psychiatry, Graduate School of Medicine, Chiba University
Satoru Esumi	Department of Pharmacy, Okayama University Hospital
Kazutaka Ohi	Department of Psychiatry, Gifu University Hospital
Hayato Ohshima	Ohshima Hospital
Tetsuro Ohmori	Aizato Hospital
Kazuto Oya	Department of Psychiatry, School of Medicine, Fujita Health University
Haruhiko Oda	Hyogo Prefecture–Hyogo Mental Health Center
Shinichiro Ochi	Department Neuropsychiatry, Ehime University Graduate School of Medicine
Masako Kageyama	Osaka University Institute for Advanced Co-Creation Studies
Tetsufumi Kanazawa	Department of Neuropsychiatry, Osaka Medical and Pharmaceutical University
Taro Kishi	Department of Psychiatry, School of Medicine, Fujita Health University
Taishiro Kishimoto	Hills Joint Research Laboratory for Future Preventive Medicine and Wellness, Keio University School of Medicine
Saya Kikuchi	Department of Psychiatry, Tohoku University Hospital
Dai Kimura	Department of Psychiatry, Graduate School of Medicine, Chiba University/ Kimura Hospital
Ichiro Kusumi	Department of Psychiatry, Hokkaido University Graduate School of Medicine
Nozomu Kotorii	Kotorii Isahaya Hospital
Kenji Sakuma	Department of Psychiatry, School of Medicine, Fujita Health University
Tsuyoshi Sasaki	Department of Child Psychiatry, Chiba University Hospital
Soichiro Sato	Kibogaoka Hospital
Hideki Sato	National Center Hospital, National Center of Neurology and Psychiatry

Enami Sawayama	Department of Psychiatry, School of Medicine, Kitasato University
Toshihito Suzuki	Mental Clinic, Juntendo University Koshigaya Hospital
Masahiro Suzuki	Nihon University School of Medicine
Taro Suwa	Department of Psychiatry, Kyoto University Hospital
Yoshikazu Takaesu	Department of Neuropsychiatry, Graduate School of Medicine, University of the Ryukyus
Hiroyoshi Takeuchi	Department of Psychiatry, Keio University School of Medicine
Yoshiteru Takekita	Department of Neuropsychiatry, Kansai Medical University
Masahiro Takeshima	Department of Neuropsychiatry, Akita University Graduate School of Medicine
Aran Tajika	Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine
Seiichiro Tarutani	Shin-Abuyama Hospital
Takashi Tsuboi	Department of Psychiatry, Faculty of Medicine, Kyorin University
Tetsu Tomita	Department of Neuropsychiatry, Hirosaki University Hospital
Atsuo Nakagawa	Clinical and Translational Research Center, Keio University
Tsutomu Nagai	Department of Hospital Pharmaceutics, Showa University School of Pharmacy, Showa University Karasuyama Hospital
Shusuke Numata	Department of Psychiatry, Tokushima University Graduate School of Biomedical Science
Kiyotaka Nemoto	Department of Psychiatry, Faculty of Medicine, University of Tsukuba
Ikuo Nomura	Moriyama General Psychiatric Hospital
Yasuhiko Hashimoto	Kobe Gakuin University
Ryota Hashimoto	Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry
Masakazu Hatano	Department of Clinical Pharmacy, School of Medicine, Fujita Health University
Akitoyo Hishimoto	Department of Psychiatry, Yokohama City University Graduate School of Medicine
Norio Furukori	Department of Psychiatry, Dokkyo Medical University
Hikaru Hori	Department of Psychiatry, Faculty of Medicine, Fukuoka University
Kentaro Matsui	Department of Laboratory Medicine, National Center Hospital, National Center of Neurology and Psychiatry
Yuki Matsuda	Department of Psychiatry, Jikei University School of Medicine
Itaru Miura	Department of Neuropsychiatry, Fukushima Medical University School of Medicine
Atsunobu Murata	Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry
Takaaki Yasuda	Mental Clinic, Saitama Medical Center
Hiroki Yamada	Mental Care Center, Showa University Northern Yokohama Hospital
Oumi Watanabe	Japan Drug Information Institute in Pregnancy, National Center for Child Health and Development

Patient members

Takashi Aizawa	Yokohama Peer Staff Association/Community Activity Support Center Space Umi
Mizume Suzuki	Yokohama Peer Staff Association
Tetsuya Fujii	Yokohama Peer Staff Association
Kenjiro Horiai	Yokohama Peer Staff Association
Yuhei Yamada	Porque Japan

Family members

Kumiko Okada	National Federation of Associations of Families with the Mental Illness in Japan (Minna-Net)
Rei Kato	Family Association for People with Mental Disabilities in Shinjuku City, Tokyo “Shinjuku Friends”
Yumiko Nakagoshi	Saitama City People with Mental Disabilities “Mokusei Family Association”/LINE Family Association “Pure Light”

Japanese Psychiatric Nurses Association member

Takuya Hatakeyama	Department of Nursing, Komazawa Women's University

Japanese Association of Occupational Therapists member

Masayoshi Kobayashi	Department of Health Sciences, School of Medicine, Shinshu University

Japanese Association of Mental Health Social Workers member

Satoshi Inami	General Support Division, Utsunomiya Hospital

Association of Japanese Clinical Psychology member

Haruo Fujino	United Graduate School of Child Development, Osaka University, Kanazawa University, Hamamatsu University School of Medicine, Chiba University, and University of Fukui

Japan Psychiatric Hospitals Association member

Takao Mori	Aisei Memorial Hospital

Japanese Association of Neuro-Psychiatric Clinics member

Eiichi Katsumoto	Katsumoto Mental Clinic

Japanese Society of General Hospital Psychiatry member

Naoko Satake	National Center Hospital, National Center of Neurology and Psychiatry

Legal committee member

Hisako Takeichi	Tokyo Bar Association

Basic medical researcher committee

Makoto Arai	Schizophrenia Project, Department of Psychiatry and Behavioral Sciences, Tokyo Metropolitan Institute of Medical Science

Japanese Society of Schizophrenia Research cooperation committee members

Emi Ikebuchi	Teikyo Heisei University Graduate School of Clinical Psychology
Kiyoto Kasai	Department of Neuropsychiatry, University of Tokyo
Masato Fukuda	Department of Psychiatry and Neuroscience, Gunma University Graduate School
Toshiya Murai	Department of Neurology (Psychiatry), Kyoto University Graduate School of Medicine

The guideline management committee comprised a co-representative and a few members representing the Japanese Society of Neuropsychopharmacology and Japanese Society of Clinical Neuropsychopharmacology. The committee's role was to clarify the purpose of creating this guideline, establish an organizational structure, and help lead the creation, publication, and dissemination of this guideline.

The guideline creation committee members comprised approximately 20 psychiatrists with extensive experience in composing guidelines for the Japanese Society of Neuropsychopharmacology and Japanese Society of Clinical Neuropsychopharmacology. Patients, family members, supporters, and individuals in related academic societies and associations participated in the discussion and evaluation as members of the guideline creation committee, not as external members, and participated interactively in the creation of this guideline. Approximately 12 psychiatrists served concurrently as leaders and deputy leaders of each systematic review team, and acted as mediators between the systematic review team and guideline creation committee. The systematic review team was in charge of the systematic review, as well as discussions as guideline creation committee members. The remaining psychiatrists formed a brush-up team and coordinated the opinions of the leaders and deputy leaders of each systematic review team, patients, families, supporters, and members of related academic societies and associations to ensure overall unity.

The composition of these committees is described at the end of this guideline.

CONFLICT OF INTEREST

The guideline creation committee made every effort to avoid actual or potential conflicts of interest to enable its members to perform their duties in a neutral and fair manner. All members and academic societies involved in guideline creation disclosed potential or actual conflicts of interest. The disclosure criteria were set according to the "Guidance on eligibility criteria for participation in the development of clinical practice guidelines" by the Japanese Association of Medical Sciences, with the target period from January 1, 2019, to December 31, 2021.

Information on the conflicts of interest of the members and organizations of the Japanese Society of Neuropsychopharmacology and Japanese Society of Clinical Neuropsychopharmacology, which created the guideline, is provided at the end of this document.

"Guideline for Pharmacological Treatment of Schizophrenia" task force meeting status

October 6, 2018	First meeting
December 23, 2018	Second meeting
May 12, 2019	Third meeting
November 23, 2019	Fourth meeting
January 13, 2020	Fifth meeting
November 14, 2021	Sixth meeting

In addition, brief online meetings were conducted regularly.

Interim report on the preparation of the guideline and public discussion.

October 11, 2019 (Friday).

Symposium "Aim and scope of Revised Guideline for Pharmacological Therapy of Schizophrenia."

Venue: 49th Meeting of the Japanese Society of Neuropsychopharmacology, Fukuoka.

Conceptualization of this guideline

(1) Target audience for the guideline

This guideline is evidence-based and is created primarily for psychiatrists who are involved in the treatment of schizophrenia. The content of this guideline was drafted with the aim of supporting psychiatrists in making decisions together with patients and their families in clinical settings, and we hope that it will be used in daily clinical practice. We plan to create a "Guide for Pharmacological Therapy of Schizophrenia" for affected individuals, their families, and supporters following the publication of this guideline.

(2) Guideline composition

This guideline consists of three main sections: Introduction, Part 1 "Formulation of schizophrenia therapy plan," and Part 2 "Clinical questions (CQs) for treatment of schizophrenia." Part 1 contains "Chapter 1: Diagnosis and differential diagnosis of schizophrenia," "Chapter 2: Treatment of Schizophrenia: Overview," and "Chapter 3: Patient-therapist decisions about long-term quality of life: Positioning of this guideline." Part 2 consists of "Chapter 1: Treatment in acute phase of schizophrenia," "Chapter 2: Treatment of schizophrenia in stable/maintenance phase," "Chapter 3: Drug-induced extrapyramidal side effects of antipsychotics," "Chapter 4: Other side effects of antipsychotics," "Chapter 5: Treatment-resistant schizophrenia," "Chapter 6: Other clinical problems 1," and "Chapter 7: Other clinical problems 2."

(3) Diagnosis of schizophrenia

In this guideline, the diagnosis of schizophrenia is assumed to be established. In actual clinical practice, the diagnosis of schizophrenia requires careful exclusion of organic disorders and other psychiatric disorders, such as mood disorders. This guideline is not applicable to patients with symptoms only similar to schizophrenia. Additionally, even if the diagnosis is schizophrenia, there are cases where the content of this guideline does not apply due to comorbidities. Diagnosis is described in Part 1 "Formulation of schizophrenia therapy plan," "Chapter 1: Diagnosis and differential diagnosis of schizophrenia." Please read this carefully and use the CQs in Part 2, which provides specific content on the topic.

(4) Need for comprehensive treatment in schizophrenia

A major premise of schizophrenia treatment is the combination of psychosocial and pharmacological treatment. Furthermore, fostering a sense of security resulting having trusting human relationships and a stable life is the basis of professional treatment. Such psychosocial treatment is mainly addressed in Part 1 "Formulation of schizophrenia therapy plan," "Chapter 2: Treatment of schizophrenia: Overview." Regarding pharmacological treatment, please understand that each CQ in Part 2 mainly addresses relevant points, and please use this guideline in a comprehensive manner.

(5) The role of the guideline in shared decision-making (SDM)

As with the treatment of all disease, the selection of treatment of schizophrenia considers the balance between the efficacy (benefits) and side effects (harms) of the treatment; with a treatment being considered useful only if its benefits outweigh the harms. Based on this ideology, this guideline is created based on the accumulated evidence on benefits and harms, thereby making appropriate recommendations. Decision-making in clinical practice should be performed jointly by medical professionals and patients, with the advantages and disadvantages of multiple treatment options shared and two-way consultations conducted between the two parties (this is called SDM); this guideline provides evidence to be shared at that time.

As described in Part 1 "Formulation of schizophrenia therapy plan," "Chapter 3: Patient-therapist decisions about long-term quality of life: Positioning of this guideline," we hope that this guideline will support SDM.

(6) One of the reference materials for decision-making in clinical practice

Clinical practice guidelines are created for the purpose of supporting patients and medical professionals, and they can be used as decision-making tools in clinical practice. Guidelines have scientific and systematic basis and contain recommendations based on evaluations of the benefits and harms of multiple treatment options; they are also updated based on latest research.

This scientific basis is called evidence, but it is only probabilistic information for patients with a certain condition. Therefore, it cannot be directly applied to individual patients. Furthermore, the patients on whom the evidence is based are often patients with schizophrenia and no comorbidities, and further details require confirmation from the papers that form the basis of this evidence. Therefore, the circumstances of each individual patient may not necessarily apply to the recommendations. Therefore, guidelines should be used with the understanding that they allow physician discretion and are not followed unilaterally. Using this guideline as evidence for making legal decisions would constitute as its misuse.

(7) Necessity of reading through the latest version

The guideline task force will update the guideline appropriately when new important information and comments are received. Please always use the latest version of the guideline (published on website).

Treatment of schizophrenia should be comprehensive, including psychosocial treatment in combination with pharmacological treatment, rather than relying on pharmacological treatment alone. Additionally, various measures are required during the course of the disease. This guideline describes pharmacological treatment based on the stage of schizophrenia. However, when using this guideline, please read it in its entirety first, rather than only reading selected sections.

(8) Guideline dissemination policy and monitoring

This guideline is published free of charge on the society website to facilitate easy access. We will also publish a book that is easy to obtain and comprehend. Furthermore, we are planning to create the "Guide for Pharmacological Therapy of Schizophrenia" for patients, families, and supporters. Through the EGUIDE project (https://byoutai.ncnp.go.jp/eguide/), which disseminates, educates, and verifies activity for psychiatric treatment guidelines, we will conduct workshops so that users can comprehensively understand the contents of these guidelines and promote the dissemination, education, and verification of this guideline. Such workshops under the EGUIDE project will promote the dissemination of the guideline. An additional factor hindering guideline dissemination is that prescription regulations are sometimes stricter in Japan than those in other countries because clozapine treatment, which is recommended for treatment-resistant schizophrenia, is not very popular in Japan compared with other countries. Additionally, the quality indicator (QI) of the guideline, which is the extent the guideline's recommendations are used (e.g., antipsychotic monotherapy rate), is evaluated through nationwide surveys. Based on the results of these evaluations, the method of dissemination and education will be reviewed annually, lectures will be held, and the guideline will be revised.

Procedure for creating this guideline

The basic process of creating this guideline is in accordance with the "Minds Clinical Practice Guideline Creation Guide 2017" of the medical information service (Minds).

As the "Guideline for Pharmacological Therapy of Schizophrenia" task force, we summarized the opinions obtained to date, determined the scope, and set the CQs based on the "Guideline for Pharmacological Therapy of Schizophrenia" (latest online version revised in 2017).

When summarizing opinions, we examined feedback from the EGUIDE project's guideline workshops and publication of the "Guideline for Pharmacological Therapy of Schizophrenia" for patients, families, and supporters. In setting the scope and CQs, the opinions of the associated parties, including the patients and their families, were combined the opinions of the specialist committee members and incorporated into the current state of psychiatric care in Japan. The CQs, including the outcome settings, were decided in a meeting on May 12, 2019.

Each working group of the guideline task force conducted a systematic review for each CQ and evaluated the body of evidence. To conduct an exhaustive search, we searched three literature databases: PubMed, the Cochrane Library, and Ichushi Web. The literature search was completed by December 2019, and the scope of the databases to be searched was expanded as needed, with already published international guidelines also referenced. This is a guideline for the treatment of schizophrenia in Japan. Therefore, only treatment and preventive methods that could be implemented in Japan within the literature search period were included. Additionally, we recorded the search formula and scope of the literature search and published them on the society website.

When integrating the body of evidence from the systematic review results, we emphasized evidence from randomized controlled trials (RCTs) (Tables 1 and 2). Cases that were based on RCTs and where the body of evidence were evaluated for the primary outcome and at least one harmful and beneficial outcome was set as **"recommendation."** Cases that had insufficient RCT-based evidence were set as **"semi-recommendation."** When integrating the body of evidence from RCTs alone, it is challenging to evaluate CQs for which an RCT is difficult to conduct or to evaluate long-term outcomes; for example; we supplemented the evidence with observational studies. Several studies with high impact evidence involve subjects with schizophrenia whose symptoms and social functions permitted them to consent to participate in research without complications. Such studies also involve a comparison of placebo and target drug monotherapy (no concomitant use of other drugs), where the drug is administered daily at the approved dose for 4–8 weeks or longer. Therefore, unless special conditions are stated, the evidence presented in this guideline is in the context of monotherapy with relevant drugs. Each working group of the "Guideline for Pharmacological Therapy of Schizophrenia" prepared draft recommendations for each CQ based on the evaluation of the body of evidence (e.g., summary of body of evidence, balance between benefits and harms/risks, cost, and resource use). To ensure the appropriateness of the systematic review of the CQs and drafting of the recommendations, internal examinations were conducted by each working group of the guideline creation task force.

The draft recommendations for each CQ were reviewed by the "Guideline for Pharmacological Therapy of Schizophrenia" task force members at the recommendation-level decision meeting while considering consistency with guidelines in other fields, and

TABLE 1 Method of systematic review and integration of body of evidence.

	Systematic review method	Integration of body of evidence	Description of recommendation (semi-recommendation)
Recommendation	• As a result of the literature search, systematic reviews and meta-analyses of RCTs were confirmed and adopted • Some outcomes were supplemented with evidence from RCTs and observational studies that were confirmed by hand search	• The body of evidence from systematic reviews of RCTs on important outcomes (at least one beneficial outcome and one harmful outcome) was integrated	• Outcomes of the body of evidence based on RCTs were described in terms of the strength of recommendation (1 = "Recommended" or 2 = "weakly recommended") and strength of evidence (Table below: A–D)
Semi-recommendation	• As a result of the literature search, sufficient evidence was not obtained for integrating the body of evidence from RCTs • We adopted the results of observational studies and expert opinions obtained by hand search	• Integration was not possible because the body of evidence for important outcomes (one or more beneficial and harmful outcomes) could not be created	• Strength of recommendation 1 or 2, and strength of evidence not described

TABLE 2 Strength of evidence.

A	Strong	Confident that the true effect is close to the expected effect
B	Moderate	True effect is thought to be close to the expected effect, but a possibility of obtaining a different result remains
C	Weak	True effect is thought to be close to the expected effect, but greater a possibility of obtaining a different result remains
D	Very weak	Estimated effect is very unclear and often far from the true effect

each draft recommendation was decided on January 13, 2020, by unanimous consensus. The guideline brush-up team examined the evidence for the approved CQs, recommendations, and commentary texts, and aimed for overall consistency and standardization of the commentary text terminology. In collaboration with the Japanese Society of Psychiatry and Neurology guideline review committee, public comments were received through the Japanese Society of Neuropsychopharmacology and Japanese Society of Clinical Neuropsychopharmacology members and cooperating organizations, and their websites, and revisions were made while incorporating these opinions.

The final version was approved by all members on April 14, 2022.

Approval by the boards of directors of both societies was obtained on April 23, 2022.

Disclaimer

This guideline was created to provide current evidence-based knowledge about the treatment of schizophrenia and to support decision-making in clinical settings. The guideline does not determine treatment, and treatment should be planned at the discretion of the therapist according to the time and situation, without being bound by the guideline. Using this guideline as the basis for the determination of legal negligence constitutes a clear misuse of this guideline.

Publication and revision

We plan to revise this guideline approximately every 4 years. The publication of the next revision is scheduled for 2026. If important findings that require content revision are obtained prior to that date, then partial revisions will be considered.

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TABLE OF CONTENTS

CQ6-1: Are sedative psychotropics recommended for insomnia symptoms in patients with stable schizophrenia?
CQ6-2: Are as-needed anxiolytics and sedatives recommended for anxiety, agitation, and insomnia in schizophrenia?
CQ6-3: Is switching or reducing antipsychotics, or reducing or discontinuing concomitant psychotropics recommended for schizophrenia with hypersomnia?
CQ6-4: What pharmacological treatment is useful for depressive symptoms of schizophrenia?
CQ6-5: Is there pharmacological treatment recommended for cognitive dysfunction of schizophrenia?

Chapter 7: Other clinical problems 2

CQ7-1: What pharmacological treatment is recommended for psychomotor agitation?
CQ7-2: What treatment is recommended for catatonia of schizophrenia?
CQ7-3: What pharmacological treatment is recommended for pathological polydipsia and water intoxication?
CQ7-4: Are antipsychotics useful for schizophrenia during pregnancy?
CQ7-5: Are antipsychotics useful for women with schizophrenia in postpartum period (including those who are breastfeeding)?
CQ7-6: Are antipsychotics useful for first-episode psychosis?

Role of members who formulated the Guideline for Pharmacological Therapy of Schizophrenia

Conflict of interest

1. Personal conflict of interest.
2. Organizational conflict of interest.

PART 1: FORMULATION OF TREATMENT PLAN FOR SCHIZOPHRENIA

Chapter 1: diagnosis and differential diagnosis of schizophrenia

Introduction

In schizophrenia, no definitive physical symptoms, laboratory findings, or biomarkers reflecting disease activity that are useful for diagnosis have been discovered; therefore, diagnosis must rely on psychiatric symptoms.[1] Schizophrenia has historically characteristic psychiatric symptoms, such as Bleuler's four A's and Schneider's first-rank symptoms for schizophrenia, but these are disease concepts and not diagnostic criteria.[2] There is no single psychiatric symptom that can definitively indicate schizophrenia in terms of diagnostic sensitivity and specificity, but characteristic psychiatric symptoms that aid in the diagnosis of schizophrenia include primary psychiatric symptoms, as well as ego disturbances, communication difficulties, and lacking insight or awareness into their illness and symptoms.[1] Ego disturbances are unique to schizophrenia, and Schneider's first-rank symptoms of schizophrenia, which is centered on ego disturbances, are useful in diagnosing schizophrenia. Communication difficulties are also important. Psychiatrists who interview patients with communication difficulties are unable to communicate with them or gain emotional empathy, and they receive a unique impression of rejection or praecox feeling. Additionally, lack of disease awareness is helpful in diagnosing schizophrenia. However, praecox feeling may not be present, and lacking awareness of illness and symptoms may also be seen in other organic brain and psychiatric disorders. Meanwhile, even patients with mild schizophrenia may have an awareness of their own abnormalities to some extent and a sense of the disease, so it is not possible to diagnose schizophrenia based on lacking awareness of illness and symptoms alone. Furthermore, having a close relative with a clear genetic predisposition to schizophrenia or some form of psychiatric disorder may aid in the diagnosis of schizophrenia.

Bleuler's four A's[1]

- Loosening of associations in thought disorders (disorganizing thought)
- Blunted affect (diminished emotional response to stimuli)
- Autism (a loss of awareness of external events, and a preoccupation with the self and one's own thoughts)
- Ambivalence (an apparent inability to make decisions, again suggesting a deficit of the integration and processing of incident and retrieved information)

Schneider's first-rank symptoms of schizophrenia[1]

- Hearing thoughts spoken aloud
- Hearing voices referring to himself/herself made in the third person
- Auditory hallucinations in the form of a commentary
- Somatic hallucinations
- Thought withdrawal, insertion, and interruption
- Thought broadcasting
- Delusional perception
- Feelings or actions experienced as made or influenced by external agents

Key aspects in diagnosis and evaluation

Schizophrenia is mainly diagnosed by interviewing the affected individual or his or her family. In medical interviews, the following questions are mainly asked:

1. What symptoms did you experience?
2. When did the symptoms start?
3. How did the symptoms progress?
4. To what extent do they interfere with your social and daily functioning?

Additionally, mental symptoms, such as consciousness, orientation, intellectual level, thoughts, and emotions, are evaluated in the interview. Information about growth history, medical history, family history, and substance use history is also important for diagnosis. If the affected individual is not aware of the disease, has difficulty communicating, or has a strong distrust of others and a frequent negative attitude, then interviewing him/her may be difficult, especially if he/she is agitated. In this case, interviewing the family is a priority. Additional parameters, such as, height, weight, vital signs, and physical and neurological findings, are assessed to ascertain physical health status. Routine tests include blood and urine tests, and ECG.

Diagnostic criteria

There are two diagnostic criteria, "DSM-5" by the American Psychiatric Association, and the International Classification of Diseases "ICD-10" by the World Health Organization (WHO).

The following tests should be conducted according to the interview and physical findings to exclude mental disorders due to physical disease. Specific physical diseases are determined through differential diagnosis.

- Blood tests (e.g., thyroid function and syphilis reaction) and urine tests
- Electroencephalography (e.g., evaluation of level of consciousness)
- Brain imaging by CT or MRI
- Other (e.g., cerebrospinal fluid test)

(1) DSM-5[2,3]

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least (1), (2), or (3) must be present.

1. Delusion
2. Hallucination
3. Disorganized speech (e.g., frequent derailment or incoherence)
4. Grossly disorganized or catatonic behavior
5. Negative symptoms (i.e., diminished emotional expression or avolition)

B. Deterioration of social and occupational functions is observed.

C. Continuous signs of the disturbance persist for at least 6 months.

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder (ASD) or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Delusion: Delusions are fixed beliefs that do not change despite evidence of the contrary. They include a variety of themes (e.g., victimization, relationships, body, religion, and exaggeration). Distinguishing between delusions and rigid thinking can be difficult. The degree of certainty that the belief is true, regardless of clear or reasonable evidence of the contrary, is thought to be one of the factors that determine the distinction between delusions and rigid thinking.

Hallucination: Hallucinations are sensory-like experiences that occur in the absence of external stimuli. Hallucinations are vivid, experienced with the same intensity as normal perception, and cannot be voluntarily controlled.

Deconstructed language: Disorganized thinking (impaired forms of thought) is commonly inferred from the affected individual's speech. The individual may stray from one topic to another (derailment or loose association). In some cases, a question may be answered with a response that has little to no relevance (no contact).

Markedly abnormal psychomotor behavior: This manifests in various ways, from child-like "stupid" behavior to unpredictable agitation. Problems are found in all goal-oriented behaviors and make it difficult to even perform activities of daily living.

Negative symptoms: The two negative symptoms reduced emotional expression and lack of motivation are particularly prominent in schizophrenia. Reduced emotional expression includes reduced facial expression, eye contact, and speech intonation (prosody), as well as reduced hand, neck, and facial movements that commonly emphasize emotion in speech. Lack of motivation is a reduction in self-directed purposeful behavior, such as sitting still for long periods of time and showing no interest in working or participating in social activities.

(2) ICD-10[4]

The general characteristics of schizophrenic disorders are basic and characteristic distortions of thinking and perception, with inappropriate or blunted effect. The patient is usually clear-headed and retains intellectual faculties, but over time some cognitive deficits may develop and evolve. The most important psychopathological symptoms include ideation, ideational blasts or deprivation, propagation of ideation, delusional perceptions and delusions of being made to think, phantom voices that criticize or talk about the patient in the form of affected or disturbed experiences, thought disorder, and negative symptoms. The course of schizophrenic disorder may be persistent or intercurrent, with progressive or continuing deficits, or one or more episodes with complete or incomplete remission.

A diagnosis of schizophrenia should not be made in the presence of significant depressive or manic symptoms unless it is clear that schizophrenic symptoms preceded the affective disorder. Schizophrenia should also not be diagnosed in the presence of obvious brain disease or during drug addiction or withdrawal. A schizophrenia-like disorder should be considered a separate disorder if there is epilepsy or other brain disease or similar disorder caused by a psychoactive substance.

Differential diagnosis[1]

Both DSM-5 and ICD-10 require the exclusion of other diseases before making a diagnosis of schizophrenia. Differential diagnoses are listed below.

1. Differentiation from short-term psychotic disorder

In this disorder, symptoms resembling schizophrenia are observed within 2 weeks after severe stress and last for only 1 day to 1 month. The cause is unknown, but is related to strong stressors. The symptoms are similar to those of schizophrenia, with hallucinations and delusions predominating, but thought disorder is rarely observed. It is characterized by acute and transient occurrence, and the patient often recovers with or without pharmacological treatment. Approximately 30% of patients diagnosed with short-term psychotic disorder progress to schizophrenia after 3 years.

2. Differentiation from schizophreniform disorder

Schizophreniform disorder is diagnosed when symptoms similar to schizophrenia persist for at least 1 month and the diagnostic criteria for short-term psychotic disorder are no longer met. If symptoms persist for at least 6 months, the diagnosis of schizophrenia is made, but some cases may progress to bipolar disorder or schizoaffective disorder, strongly implying a provisional diagnosis of schizophreniform disorder. One-third of patients ultimately diagnosed with schizophreniform disorder recover within 6 months, and two-thirds are subsequently diagnosed with schizophrenia or schizoaffective disorder.

3. Differentiation from delusional disorder

In delusional disorder, delusions are persistent, but other psychiatric symptoms are rarely observed. The contents of the delusion are not outlandish and can be real, such as being followed or poisoned; and hallucinations associated with the contents of the delusion, if present, are transient or fragmentary. Excluding the direct effects of delusions, the impairment of psychosocial functioning is more localized than that experienced with other psychotic disorders, such as schizophrenia, and the behavior is not peculiar or bizarre.

4. Differentiation from schizoaffective disorder

Active phases of schizophrenia and mood episodes co-exist in schizoaffective disorder, and mood symptoms must be present for at least half of the active phase. The presence of delusions or hallucinations can occur for ≥2 weeks without mood episodes over the course of the illness. Negative symptoms and lack of insight are milder than that experienced with schizophrenia.

5. Differentiation from mood disorders

Differentiation is sometimes difficult because the mania and depression of bipolar disorder resemble the positive and negative symptoms of schizophrenia, respectively. A major difference is that schizophrenia is a disorder of "thinking" whereas manic depression is a disorder of "mood." Thus, when symptoms fluctuate in relation to mood, bipolar disorder can be differentiated from schizophrenia.

6. Differentiation from personality disorders

Personality disorders include schizotypal personality disorder, characterized by social and emotional rejection of others and quirks in thinking, cognition, and speech. Symptoms similar to those of schizophrenia may occasionally occur, but the severity of symptoms is milder than that of schizophrenia, and the diagnostic criteria for schizophrenia are not met. If the criteria are met before the onset of schizophrenia, then this is described as "schizophrenic personality disorder (premorbid)." Patients with other personality disorders may also present with temporary hallucinations and delusions, and these disorders should be differentiated.

7. Differentiation from psychiatric symptoms arising from physical conditions

Psychiatric symptoms resembling schizophrenia can result from physical conditions, such as brain tumors, viral encephalitis, temporal lobe epilepsy, delirium, thyroid disease, and carbon monoxide poisoning. These conditions can often be clearly diagnosed via brain imaging and cerebrospinal fluid examination. Epileptic twilight states may involve delusional hallucinations resembling schizophrenia, psychomotor agitation, and stupor; and when the twilight state persists for several days or weeks, differentiation from schizophrenia may be difficult. Acute psychomotor agitation due to encephalitis or carbon monoxide poisoning may be difficult to differentiate from catatonic schizophrenia. Young women with early stages of anti-NMDA receptor encephalitis are particularly likely to exhibit depression, lethargy, etc., followed by hallucinations, delusions, convulsions, memory impairment, and amnesia similar to schizophrenia, thereby making it difficult to distinguish from schizophrenia. Encephalitis sequelae may be difficult to differentiate from schizophrenia due to parkinsonism-induced hypomimia, reduced mobility, and occasional hallucinations and delusions. It may be difficult to differentiate dementia from schizophrenia due to dementia-induced delusions of theft and psychomotor agitation.

8. Differentiation from psychotic symptoms resulting from substance use (e.g., drugs, alcohol, and psychotropics)

Psychostimulants, such as cocaine, nicotine, caffeine, amphetamines and methamphetamines, MDMA, and methylphenidate, can cause hallucinations and delusions; thus, a history of drug use is important information. Poisoning psychoses caused by so-called "awakening amines," such as methamphetamine, involve almost no disturbance of consciousness, and the psychotic symptoms are very similar to those of schizophrenia. Although there are some differences, such as fewer communicative disorders with poisoning psychoses, differentiation is

often difficult using psychotic symptoms alone. Alcohol, organic solvents, benzodiazepine receptor agonists, opioid drugs (e.g., heroin, opiates, and morphine), and cannabis are classified as central nervous system depressants, and it may be difficult to differentiate their effects from schizophrenia when the disturbance of consciousness is mild. Asking about drug history is also important because psychotic symptoms may occur due to the use of delirium-inducing drugs, such as corticosteroids, H_2 blockers, and psychotropics (antidepressants and benzodiazepine receptor agonists).

9. Differentiation from dissociative disorder

Delusional hallucinations and stupor may occur during dissociative disorder, and these may need to be differentiated from schizophrenia. This type of dissociative disorder occurs in normal social life, but it often appears as a reaction to detention in prisons. Dissociative disorder has a psychological cause, and it can be differentiated by the fact that the subsequent progression of symptoms parallels changes in surrounding circumstances and that there are certain features of psychogenic reactions, such as exaggeration and elevated suggestibility, in the clinical picture.

10. Differentiation from intellectual disability / developmental disability

Patients with mild intellectual disabilities are prone to dissociative disorders due to psychogenic causes and sometimes present with catatonic agitation or stupor-like states. However, they can be differentiated by the presence of mental retardation, presence of psychogenic causes, and short-term psychiatric symptoms. The differentiation between grafting schizophrenia, in which schizophrenia occurs on top of intellectual disability, and the dissociative disorder described above may not necessarily be straightforward, but is confirmed through various psychiatric symptoms unique to schizophrenia.

Developmental disorders include ASD and attention-deficit/hyperactivity disorder (ADHD), both of which are usually present in early childhood. Meanwhile, schizophrenia patients exhibit the appearance of characteristic symptoms that were absent before puberty. Hallucinations and delusions are also observed in developmental disorders, but they are often transient and do not persist as in schizophrenia.

Subclassifications

Important subclassifications for establishing treatment strategies for schizophrenia include the presence or absence of treatment-resistant schizophrenia and cognitive decline. For these cases, evaluations are necessary because the recommended treatment differs depending on the presence of these conditions. Please refer to the applicable CQs in Part 2 for details of these evaluations and therapies.

Conclusions

The diagnosis of schizophrenia is made by physicians mainly by evaluating the clinical course and psychiatric symptoms, but there are many cases in which the evaluation of psychiatric symptoms is difficult. Therefore, it is desirable to develop an auxiliary diagnostic method that can objectively evaluate the characteristics of schizophrenia. Additionally, patients with schizophrenia who lack awareness of illness and symptoms, such as hallucinations and delusions that are used by physicians for their diagnosis, as facts that are based on the patients' subjective experiences. Thus, there are cases where the patients may find it difficult to trust the physician's diagnosis and receive treatment. If an objective auxiliary diagnostic method is developed, then it is expected that patients with schizophrenia could be more persuaded to receive treatment earlier.

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CHAPTER 2: TREATMENT OF SCHIZOPHRENIA: OVERVIEW

RECOVERY AS A TREATMENT GOAL

Recently, recovery has been the goal of the treatment of schizophrenia. Recovery has both subjective and objective aspects for the individuals involved, and their definitions and methods of assessment remain controversial. Essentially, it is important to maintain clinical recovery as a symptomatic remission, prevent relapse, and support the process of functional recovery and personal recovery while maintaining mental and physical health.[1,2] The median proportion of patients with schizophrenia who achieve both clinical recovery and functional recovery has been reported 13.5%.[3] In order for as many patients as possible to achieve recovery, the development of more effective support strategies and treatment methods is anticipated.

BIOLOGICAL AND PSYCHOSOCIAL THERAPIES FOR RECOVERY

Achieving the treatment goal of recovery for patients with schizophrenia necessitates a comprehensive approach that integrates a broad spectrum of biological and psychosocial treatments. This approach requires the collaboration of patients, their families, and other supporters, and a multidisciplinary team of healthcare professionals.[4] Healthcare professionals can enhance their support by learning about the patient's life circumstances outside of the medical setting from their families and other supporters.

Biological treatment, which includes pharmacological and electroconvulsive therapies, acts directly on the brain and promotes functional recovery of the central nervous system.

Psychological treatment or psychotherapy mainly employs verbal communication to effect changes in thoughts, feelings, and behaviors. Not only specialized psychotherapies, such as psychoeducation, cognitive behavioral therapy (CBT), cognitive remediation therapy (CRT), and social skills training (SST) administered by well-trained professionals, but also the basic attitudes and approaches of daily support play significant roles.

Social treatment acts on the individual as a whole and balances the state of mind through mind–body interactions. Maintaining a regular daily routine is fundamental, and this represents one of the significant aspects of inpatient treatment. Moreover, psychiatric rehabilitation strategies including occupational therapy, psychiatric day care, and vocational rehabilitation provide regular routines and social connections. Beyond medical services like assertive community treatment (ACT) and home-visit nursing, comprehensive support utilizes a wide array of social resources, including welfare services, consultation support services, employment system disability welfare services, group homes, public employment security offices, public health centers, peer and family support, family associations, and patient associations.

PHARMACOLOGICAL TREATMENT

1. Overview of antipsychotic treatment

Pharmacological treatment of schizophrenia is primarily based on antipsychotics. The main pharmacological effect of antipsychotics is the modulation of neurotransmission via dopamine D_2 receptors. Some antipsychotics affect not only dopamine D_2 receptors but also serotonin receptors, α_1 receptors, muscarinic receptors, among others. The drug's affinity for various receptors can shape its characteristics.

A definitive clinical effect of antipsychotics in schizophrenia is the reduction in psychiatric symptoms, as evaluated using the Positive and Negative Syndrome Scale (PANSS).[5] Long-term treatment with antipsychotic medications has also been shown to reduce relapses of schizophrenia and prevent the deterioration of the patient's quality of life (QOL).

Dopaminergic system-related side effects of antipsychotics include (1) extrapyramidal side effects (e.g., parkinsonism, tardive dyskinesia, and tardive dystonia), (2) sexual dysfunction due to hyperprolactinemia (e.g., menstrual disorders, lactation, and ejaculation disorders), and (3) malignant syndrome. Other side effects affecting the nervous system include (1) weight gain and disorders in lipid and glucose metabolism, (2) constipation, and (3) cognitive dysfunction.

Pharmacological treatment of schizophrenia should be an integrated approach that manages psychiatric symptoms and preventing relapse, while carefully adjusting the necessary drug dosage and targeting the recovery of social function and improvement in cognitive function. The balance between efficacy and side effects is crucial, and a careful consideration should be given to the benefits and drawbacks of long-term administration. The life expectancy of patients with schizophrenia is 10–25 years shorter than that of the general population.[6] This can be attributed to factors such as unhealthy lifestyles, inadequate treatment of physical illnesses, high suicide rates, and the side effects of antipsychotic treatment. Antipsychotics can induce weight gain, hyperglycemia, dyslipidemia, and cardiovascular disorders. Even if antipsychotic medication improves psychiatric symptoms and prevents relapses, thereby enabling a healthier lifestyle and proper management of physical illnesses, it may still increase the risk of physical illnesses. Preference should be given to antipsychotics with relatively lower risks, and continuous monitoring the patient's metabolic and cardiovascular systems should be implemented.

2. Importance of adverse effects on antipsychotic adherence

Antipsychotics are known to mitigate both positive and related negative symptoms in patients with schizophrenia, as well as prevent relapses. However, medication adherence is often identified as a primary factor leading to relapse. Good adherence to medication can prevent relapses and increases the likelihood of remission and recovery.[7]

Antipsychotics have an optimal dosage: the antipsychotic effect is diminished if the dosage is too low, and adverse effects, such as akathisia, extrapyramidal symptoms, depression, and discomfort, are likely to occur when the dosage is too high. In addition to these adverse effects, poor efficacy of antipsychotics may further reduce adherence due to a lack of insight associated with schizophrenia. All of these factors can lead to relapses and obstruct remission and recovery.

Long-term adherence to antipsychotics is crucial for preventing relapse in schizophrenia. However, persistent adverse effects include tardive dyskinesia, tardive dystonia, and dopamine hypersensitivity psychosis. The precise mechanisms behind these adverse effects are largely unclear, but consistent or repeated excessive blockade of dopamine D_2 receptors is the most likely cause.[8] Moreover, dopamine hypersensitivity psychosis is believed to be a significant risk factor for developing treatment resistance.[9] To fully comprehend the implications of long-term continuous use and possible side effects, scientific and theoretical discussions, followed by evidence collection, are necessary.

3. Limitations of antipsychotic treatment

In pharmacological treatment of schizophrenia, the principle of using a single antipsychotic medication at the optimal dose should be adhered to in order to achieve the best therapeutic effect. Approximately 30% of patients with schizophrenia reportedly respond poorly to antipsychotics.[10] Despite antipsychotic resistance, striving for improvements in positive symptoms and impulse control with antipsychotics may result in high-dose polypharmacy. We

should refrain from administering high-dose antipsychotics solely for the purpose of improving positive symptoms. In these cases, clozapine, the only drug indicated for treatment-resistant schizophrenia, might be effective.

Schizophrenia symptoms include not only positive symptoms such as hallucinations and delusions but also negative symptoms such as loss of motivation, social withdrawal, and emotional flattening, as well as cognitive impairments like deficits in attention, memory, executive function, and social cognition. Prominent positive symptoms are expected to improve with biological-level therapies, such as antipsychotics and modified electroconvulsive therapy, and there are hopes for improvements in secondary negative symptoms and cognitive impairment associated with ameliorated positive symptoms. Negative symptoms and cognitive impairment caused by antipsychotics can also be improved through dose optimization and medication changes. However, the improvement in primary negative symptoms and cognitive impairment due to pharmacological treatment is limited, leading to decreased social function and impairment in many aspects of life.[11] Especially, as schizophrenia often develops during adolescence and young adulthood (AYA generation), resulting in insufficient social experiences, this leads to social impairment. An important theme for lifelong schizophrenia treatment is supporting patients and improving negative symptoms and cognitive impairment, in addition to preventing the relapse of positive symptoms.

PSYCHOSOCIAL TREATMENT

In this guideline, clinical questions (CQs) pertaining to psychotherapy and psychosocial treatment are not addressed. However, further improvements are anticipated by integrating these treatments with pharmacological treatment.[12] Recent studies report that dealing with difficulties is significantly related to clinical, functional, and personal recovery; involving coping with stress, problem-solving, learning ways to control unpleasant feelings and thoughts, and getting support from friends and family.[2] Therefore, enhancing the ability to cope with problems directly promotes recovery through direct patient intervention, patient-led rehabilitation, and involvement with supporters such as family members. Current techniques include psychoeducation, CBT, CRT, SST, vocational rehabilitation, ACT, peer support, and family support.[13]

Psychoeducation is defined as "an approach for assisting people with challenges that are hard to accept, such as mental disorders and AIDS, in leading a recuperative life by sharing accurate knowledge and information, considering psychological aspects, and learning how to deal with various problems and difficulties caused by illness and disability".[14] In other words, it involves learning how to handle difficulties by utilizing shared accurate knowledge and information, considering the psychological background. Specifically, the first step is listening to the individual's struggles, providing appreciation and affirmation, and collaboratively addressing these issues. Regarding drug treatment, the usefulness and challenges of pharmacological treatment, along with strategies maintaining drug adherence, could be shared.

In Japan, group-based family psychoeducation has a long history, rooted in family communities across various regions. Psychoeducation can be delivered through various combinations of style (individual and group), target (family, patient, and family including patient), and provider (professional, experienced family member, and patient), each with unique benefits. The goal of family psychoeducation is to support patient recovery by providing up-to-date information on diseases, therapies, and available social resources. The structure of psychoeducation is somewhat established, but integrating the content of this guideline as the latest and most accurate information will further enhance psychoeducation's usefulness for patients and their families.

CBT for schizophrenia primarily comprises CBT for psychosis (CBTp) and recovery-oriented CBT (CBT-R). CBTp aims to alleviate the distress associated with symptoms by understanding psychotic symptoms such as delusions and hallucination, enhancing the sense of control over these symptoms, and strengthening flexible thinking and coping behavior. CBT-R focuses on functional improvement by identifying the lifestyle desired by the patient and promoting adaptive lifestyles to achieve it. Both approaches aim for patient-desired recovery by enhancing personal functionality.

CRT is also known as cognitive function rehabilitation or cognitive training, is a method that directly approaches the cognitive impairments common in schizophrenia (i.e., attention, memory, language, and executive functions).[15,16] Although the effect size of CRT alone is small, combining it with other psychiatric rehabilitation methods, such as SST, has been reported to improve social functioning.[17] After symptom amelioration, improving cognitive function plays a vital role in achieving patient-desired life and recovery, such as returning to work or school.

SST refers to "social skills training." The goal of SST is to acquire basic skills for managing social life through role-playing based on actual situations. In Japan, "inpatient social skills training" is a covered medical expense. SST is also addressed as a form of CBT as it was developed by integrating cognitive elements into behavioral therapy, and it has been reported to improve negative symptoms and functional capabilities.[18] In addition to social skills focused on interpersonal relationships, skill packages have been developed to improve illness self-management skills, such as medication and symptom self-management. The aim is to improve the patient's self-coping ability (empowerment) and recovery.[19]

Vocational rehabilitation includes employment support and pre-employment training. Both in occupational therapy introduced in the acute phase and psychiatric daycare in the recovery phase, employment is often a long-term goal for the patients. In terms of work, step-by-step employment support based on clinical and functional recovery is considered, but the individual's motivation to work is also important. Even if a patient has symptoms, the Individual Employment Support Program provides support aiming at regular employment based on the patient's wishes and preferences. This is a recovery support program practiced in various parts of Japan along with ACT.[20]

ACT is a care management model that provides comprehensive visit-type support enabling even those with severe mental illness to

achieve and maintain their own lives in the community. Outreach, provided by a multidisciplinary team comprising nurses, mental health social workers, occupational therapists, psychiatrists, and sometimes peer staff, is implemented 24 hours a day, 365 days a year to support community life.[21]

In Japan, with the maturity of self-help organizations (support systems that do not include specialists), such as families and patient's associations, peer support for people with mental illness has also been fulfilled. The terms "peer counseling" and "peer listening" are becoming more common, and some organizations are providing training peer supporters. These organizations are often led by patients with professional qualifications and stakeholder functioning as peer staff. In many informal situations, patients support each other emotionally aiding their recovery. While peer activities can anticipate various difficulties, it is crucial to ensure that mutual support does not cause individuals involved to deteriorate mentally or confuse the ends with the means.

Family support involves providing emotionally sensitive counsel to reduce stigma. It is known that the emotional expression of a family increases when faced with difficulties associated with a family member's illness, and accepting the feelings of the family is the first step of support. Family support for schizophrenia arose partially from family therapy, which focused on interactions (communication) between individuals, and is based on the concept of "supporting alongside the family." If the family devises coping methods in various situations and demonstrates the ability to support the patient, this will lead to recovery for both the patient and family. Not only professionals are involved in family support. Traditionally, a culture of mutual support has been fostered through family classes at public health centers and local family associations in Japan, and these experiences form the basis for self-help and peer support.

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CHAPTER 3: THINKING ABOUT THEIR LIFE TOGETHER WITH PATIENTS: POSITIONING OF THIS GUIDELINE

INTRODUCTION

As defined by the Japan Council for Quality Health Care Evidence-Based Medicine (EBM) and Guideline Promotion Project (Minds), a clinical practice guideline is a "document that assesses evidence through systematic review, balances benefits and risks, and presents what is believed to be the optimal recommendations to aid health care users and providers in making decisions on significant health issues".[1] At present, these guidelines not only address treatment but also encompass a broad range of topics related to prevention, rehabilitation, nursing intervention, and social support. Increasingly, there have been efforts to facilitate the utilization of these guidelines by developing additional "public-friendly guidelines" or providing mobile and online applications as support tools.

Minds asserts that "it is desirable for individuals with various backgrounds, including patients and citizens, to participate in the creation of these guidelines".[1] Other ways in which healthcare users can contribute include evaluating drafts as external reviewers and cooperating

in interviews and surveys.[2] Although the emphasis on patient and public involvement (PPI) in clinical practice guidelines creation started in the 1990s, the focus has now shifted toward the quality standards of guidelines. In essence, shared decision-making (SDM) is practiced between healthcare users and providers throughout the development of guidelines and continues to be applied in healthcare settings based on the finalized guidelines.

During the revision of the "Guideline for Pharmacological Therapy of Schizophrenia," patients diagnosed with schizophrenia and their family members were involved as committee members. It is acknowledged that, similar to regular healthcare, user perspective should be respected in guideline development. However, executing the collaborative work posed various challenges and was not an easy process. In this section, we first introduce the significance of PPI in the process of creating clinical practice guidelines[1] and then describe how patient and family committee members actively contributed to the project.

IMPORTANCE OF PPI

1. Importance of supporting shared decision-making (SDM) integral to clinical practice guidelines

Firstly, clinical practice guidelines must meet the needs of patients. Even if a scientifically validated treatment is available, users will not benefit if they cannot access the treatment due to barriers such as high costs or limited access. Furthermore, the assumptions of healthcare providers and the values of patients and their families, who are the users, may not always align when choosing from multiple treatment options. Patient and support groups, will have diverse opinions, and there will also be unheard perspectives from individuals who do not belong to such groups.

Considering these assumptions, participating healthcare users are expected to present both their own earnest experiences and those gained from the experiences of others and accumulated group discussions. This exchange of broader perspectives, derived from diverse opinions, hopes, and values, helps to clarify the universal needs of patients and their families.

Even though they are collectively referred to as "healthcare users," the intentions of the caregiving family members do not always align with the patients' wishes. In instances of differing opinions, the patient's needs should be prioritized to uphold their rights, even if the caregiver's opinion is considered. A careful decision-making process is required where differences are acknowledged, and the root of the disagreement is discussed together, and the patient's interests are given precedence.

The most crucial aspect of SDM using clinical practice guidelines in a healthcare setting is that the guideline content should be comprehensible to involved healthcare users, such as patients and their families. Without user-friendly clinical guidelines, SDM cannot be achieved.

2. Importance of contributions developing high-quality clinical practice guidelines

Including healthcare users in the process of developing clinical practice guidelines is expected to enhance the guideline quality. The significance of user participation is discussed below. Firstly, users are expected to address issues and questions that are vital to patients but often neglected by medical professionals. Secondly, they can provide insights on topics to be tackled based on their lived experiences as patients.

As a result, medical staff can appreciate the actual impact of each treatment method on the patient and assess the benefits and risks more accurately. Recommendations can reflect patient's viewpoints, supplementing, reinforcing, or challenging the evidence. The clarity and patient-respectfulness of the final recommendation document can be assessed. Most importantly, suggestions can be made for disseminating and utilizing of clinical practice guidelines.

3. Serving as a basis for social reliability of clinical practice guideline

Clinical practice guidelines can only be seen as socially reliable when they are also developed from the user's perspective. The active participation of healthcare users in guideline formulation increases their social reliability.

INVOLVEMENT OF PATIENTS AND FAMILIES IN REVISING THE "GUIDELINE FOR PHARMACOLOGICAL TREATMENT OF SCHIZOPHRENIA"

The revision of this guideline saw the participation of psychiatrists administering therapies, alongside nurses, public health nurses, pharmacists, occupational therapists, mental health social workers, clinical psychologists, certified psychologists and other medical professionals, lawyers, as well as patients diagnosed with schizophrenia and their families; all playing roles in PPI. Specifically, they partook in review meetings as members of the guideline creation committee and participated throughout the process, including conflict of interest (COI) declaration.

This was a complex process. Each patient and family committee member needed to understand the key points of the extensive guideline descriptions, confirmed the draft filled with technical terms, and documented their questions before attending meetings. Prior to the time-intensive formulation meetings, the patient, family, and medical staff committee members met several times to review the content and held "preparatory meetings" to clarify questions before the full committee meetings. Despite adjustments to the font size and volume of the meeting materials, they were still substantial, requiring careful preparation. To allow sufficient time for discussions about content, meetings included breaks to alleviate fatigue from lengthy discussions.

1. Scope creation: Providing information on important issues and questions for patients

Various opinions were put forth regarding what should be included in this guideline when its scope was decided. The guideline's role in schizophrenia treatment was especially emphasized. Although this guideline is limited to the pharmacological treatment of schizophrenia, psychosocial approaches also play a significant part. It was reaffirmed during meetings that an overview of the therapies should be carefully described in Part 1 to avoid giving a biased impression that only pharmacological treatment is important.

2. Formulation of clinical questions (CQs): Encouraging discussions to avoid overlooking important outcomes for patients and their families

When formulating the CQs, several suggestions regarding side effects, pregnancy, childbirth, and the inclusion of committee members were incorporated. In developing the PICO (Patient, Intervention, Comparison, Outcome) framework, patients, and family members first understood the concept of "PICO," interpreted what was written, and consequently suggested modifications to the settings of P and I, as well as to the significance of outcomes. For instance, one opinion about weighting outcomes stated: "It is more crucial to consider whether individuals die from side effects than whether a drug is effective. As long as the patient is alive, measures can be taken." Once articulated, this seems like an obvious viewpoint to anyone. However, it served as a significant revelation to medical professionals, who knew about the rare side effects but were operating under the assumption that treatment efficacy is paramount. There were also opinions about side effects that impact patients' lifestyle, even if they occur less frequently and are less severe (e.g., pharmacological treatment during pregnancy and lactation and the "psychological stress of taking medication in an environment where breastfeeding is recommended"). Meanwhile, it became clear that for some outcomes, like long-term prognoses, there is insufficient evidence, even for outcomes that are important to patients and their families, suggesting the need for future research.

3. Systematic review (SR): Emphasizing on patient / family values, desires, and critical points

There were few research studies that could contribute to guidelines development on the practical topics identified by patient / family committee members during the CQ formation. Many exchanges occurred with the systematic review team. A separate working group was created for the CQs on pregnancy and lactation, which were of particular concern. Patient committee members also participated and expressed their opinions. Additionally, when a family member shared their views on a specific CQ, they were mindful of their position as a healthcare user and caregiver, stating that, "the patient might hold a different view, but as a family member, this is how I see it." This demonstrated the importance of allowing space for discussion based on the understanding that each person's perspective and values are unique, instead of lumping everyone together as "healthcare users."

4. Crafting recommendation: Incorporating values and preferences in assessing benefits and risks for patients, ultimately important outcomes, and the strength of recommendations

Throughout the recommendation drafting process, numerous opinions were shared, not only about the contents of the recommendations but also about whether the resulting text was comprehensible and included necessary information for healthcare users. For instance, in "CQ2-2: Is antipsychotic dose reduction recommended for stable schizophrenia?," patients and family members positively suggested, "if there is a dosage guideline for dose reduction, then including this in the recommendation would make it more practical." In the criteria set in advance for these guidelines, the specific dose was not recommended but explained in the commentary. After thorough deliberation among the management committee and systematic review team members, we agreed upon a phrasing that would be correctly interpreted an included it in the recommendation.

THE "GUIDE FOR PHARMACOLOGICAL TREATMENT OF SCHIZOPHRENIA": A RESOURCE FOR PATIENTS AND FAMILIES

In the first edition of the "Guide for Pharmacological Therapy of Schizophrenia," an additional document entitled "Guide for Pharmacological Therapy of Schizophrenia: For Patients, Families, and Supporters" was developed for practical use in clinical settings as a tool for decision-making (SDM).[3] Many patients and family members who participated in this process were also contributed to the formulation of this additional document. During this process, the importance of developing clinical practice guidelines that could serve as the foundation for SDM was appreciated. It was expected that participating in the revision work would be relatively straightforward. However, recognizing the structure and volume of the first edition, it was clear that adding new items to revise the guideline would require considerable effort. It is hoped that the "Guide for Pharmacological Treatment of Schizophrenia 2022" will be established as an additional document following this guideline, with an expanded scope of patient and family member involvement, and an increased number of participants.

CONCLUSION

The patient and family members who participated in this process were connected by the disease "schizophrenia," but they each had diverse backgrounds and values. They carried out public awareness activities, such as giving lectures on the use of the "Guide for Pharmacological Therapy of Schizophrenia" at patient associations, family associations, and psychiatric conferences. They consulted

with their primary psychiatrists using the knowledge gained from their involvement in developing the guideline. At the same time, they personally understood circumstances where treatment was not provided in line with the guidelines. Some patient committee members got married while working on this revision, which further deepened their interest in pregnancy, childbirth, and parenting. A patient committee member said, "I would like communicate others through the guidelines that even if you have been ill once, it does not mean that your life is stuck. With appropriate treatment and support, you can live your own life, even as a patient." Some family members reminisced about the time of disease onset and relapse, while others thought of their grandchildren growing up. These were also life reflections. It is believed that, through this series of tasks, we have come a little closer to the fundamental principle outlined in the "Schizophrenia Recovery Support Guide"[4]: "(1) support for recovery in life, (2) work on co-creation with the patients and their families as the main actors, and (3) encourage the growth of professionals who can change practice in the field."

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PART 2: CLINICAL QUESTIONS (CQS) FOR TREATMENT OF SCHIZOPHRENIA

CHAPTER 1: TREATMENT IN ACUTE PHASE OF SCHIZOPHRENIA

CQ1-1: ARE ANTIPSYCHOTICS USEFUL IN ACUTE PHASE OF SCHIZOPHRENIA?

Recommendation

Antipsychotic treatment in acute phase of schizophrenia improved overall psychiatric symptoms (A), improved positive symptoms (A), improved negative symptoms (A), reduced discontinuations (A), and improved quality of life (QOL) (A). Meanwhile, increased body weight (A), elevated prolactin levels (A), prolonged QTc intervals (A), increased use of antiparkinsonian drugs (A), and increased incidence of sedation (A) were observed, and all adverse events increased (A).

Based on these evidences, in consideration of efficacy and safety, we recommend antipsychotic treatment in acute phase of schizophrenia (1A).

Commentary

Antipsychotics are commonly used to treat schizophrenia in clinical psychiatric settings. All psychiatrists know that antipsychotic treatment is effective in acute phase of schizophrenia, but there are cases in which the patients, family members, and supporters are not fully informed. Therefore, in this CQ, we have reviewed the evidence for the effectiveness of antipsychotics in acute phase of schizophrenia, in terms of symptom improvement and safety including side effects (adverse events) and continuation of administration, and determined recommendations. The meta-analysis by Leucht et al.,[1] which is in agreement with this CQ, compared antipsychotics and a placebo in 167 randomized controlled trials (RCTs) in 28 102 patients on the outcomes indicated below. This meta-analysis did not include studies with treatment-resistant schizophrenia, first-episode schizophrenia, schizophrenia with negative or depressive symptoms dominantly, and schizophrenia with comorbid psychiatric disorders, as well as studies that had relapse prevention as the primary outcome.

The standardized mean difference for improvement in overall psychiatric symptoms was 0.47 (95% confidence interval (CI): 0.42–0.51, *N* (number of studies) = 105, *n* (number of patients) = 22 741), the number needed to treat was 6 (95% CI: 5–8), and the degree of improvement with antipsychotics was high (A). Additionally, the proportion of patients who showed effectiveness was 51% (95% CI: 45–57) for antipsychotics and 30% (95% CI: 27–34) for placebo, with a higher improvement rate for antipsychotics. For the improvement in positive symptoms, the standardized mean difference was 0.45 (95% CI: 0.40–0.50, *N* = 64, *n* = 18 174), with a higher improvement for antipsychotics (A). For the improvement in negative symptoms, the standardized mean difference was 0.35 (95% CI: 0.31–0.40, *N* = 69, *n* = 18 632) (A). Additionally, regarding improvements in QOL, the standardized mean difference was 0.35 (95% CI: 0.16–0.51, *N* = 6, *n* = 1900), with a higher improvement for antipsychotics (A).

Regarding safety outcomes, the results of comparing each safety outcome with a placebo are as follows. The rates of treatment discontinuations were 38% and 56% for the antipsychotics and placebo, respectively; the risk ratio was 1.25 (95% CI: 1.20–1.31, *N* = 105, *n* = 22 851); and the number needed to treat was 11 (95% CI: 9–14), with a lower rate of discontinuation for antipsychotics (A). For body weight, the standardized mean difference was −0.40 (95% CI: −0.47 to −0.33, *N* = 59, *n* = 17 076), with significantly increased body weight for antipsychotics (A). The rates of use of antiparkinsonian drugs were 19% and 10% for antipsychotics and placebo, respectively; the risk ratio was 1.93 (95% CI: 1.65–2.29, *N* = 63, *n* = 14 942), and the number needed to treat was 12 (95% CI: 9–16), with the use of antiparkinsonian drugs being higher for antipsychotics (A). For prolactin levels, the standardized mean difference was −0.43 (95% CI: −0.55–-0.30, *N* = 51, *n* = 15 219), with prolactin levels being elevated for antipsychotics (A). For QTc interval prolongation, the standardized mean difference was −0.19 (95% CI: −0.29–-0.08, *N* = 29, *n* = 9883), with a prolonged QTc interval observed for antipsychotics (A). The rate of sedation was 14% and 6% for the antipsychotics and placebo, respectively, and the risk ratio was 2.80 (95% CI: 2.30–3.55, *N* = 86,

$n = 18\,574$), with a higher rate for antipsychotics (A). Therefore, all adverse events increased (A).

Although the effective dose differed for each antipsychotic, many antipsychotics were effective for patients in acute phase of schizophrenia. However, it was found that the safety outcomes varied from those with no significant difference compared with the placebo to those with a significant increase in adverse events compared with the placebo.

Treatment options other than antipsychotic treatment are limited for patients in acute phase of schizophrenia. Therefore, it is necessary to fully consider gain/loss of long-term treatment with antipsychotics compared with medical costs of schizophrenia and adverse events, medical costs such as hospitalization due to relapse, and occupational and economic losses due to deterioration of social functions.

Based on these evidences, considering effectiveness and safety, we recommend antipsychotic treatment in acute phase of schizophrenia (1A).

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CQ1-2: WHICH IS MORE APPROPRIATE SWITCHING ANTIPSYCHOTICS OR INCREASING DOSE, IN CASE THAT ANTIPSYCHOTICS ARE INEFFICACIOUS IN ACUTE PHASE OF SCHIZOPHRENIA?

Semi-recommendation

In case that antipsychotics are inefficacious for patients in acute phase of schizophrenia, the dose should be increased to a sufficient level to improve psychiatric symptoms and switching from one antipsychotic to another may improve psychiatric symptoms.

Based on the above, in cases that antipsychotics are inefficacious, it is advisable to consider increasing the dose to a sufficient level or switching the medication.

Commentary

Even though the question of whether it is more beneficial to increase or switch antipsychotics for patients in acute phase of schizophrenia is a fundamental clinical question, there is currently no supporting evidence based on direct comparisons.

1. Whether to increase the dose of antipsychotics or continue at the current dose

The clinical question of whether to increase the dose of the antipsychotics or continue at the current dose was discussed in a Cochrane Review by Samara et al.[1] This review included 10 randomized controlled trials (RCTs) (mean follow-up period after increased dose: 6.3 weeks), but not only were there various doses at baseline, but some doses in the increased dose group exceeded the recommended dose range. There was no significant difference between the two therapies in terms of improvement in psychiatric symptoms, treatment discontinuations, or occurrence of adverse events. There was only one study [n (number of patients) = 17] that mentioned quality of life (QOL), but this study also showed no difference between the two groups.[2] However, 9 of the 10 RCTs examined in that review were conducted overseas, and it should be noted that the baseline dose was often equivalent to a dose ranging from sufficient to high in terms of the approved dose in Japan.[3-6] With this in mind, the results of these RCTs suggest that there is little need to increase the dose in cases where the effect is insufficient despite the fact that sufficient doses have already been administered.

In one RCT ($n = 103$) that targeted schizophrenia in Japan,[7] cases with insufficient effect despite administration with 10 mg/day olanzapine or 3 mg/day risperidone were assigned to two groups (one in which the dose of the administered antipsychotic was doubled, and the other in which the dose was maintained), and follow-up was conducted for 4 weeks. The results showed that there was no significant difference in the improvement in psychiatric symptoms between the two groups (mean difference = 0.70, 95% CI: −2.34–3.74, $p = 0.22$). Additionally, in the group with low blood concentration of the drug at baseline ($n = 29$), there was a negative correlation observed between the intensity of positive symptoms (evaluated using the positive scale of the Positive and Negative Syndrome Scale [PANSS]) and olanzapine blood concentration (Spearman $\rho = -0.48$, $p = 0.042$). An increased dose in the group whose blood concentration was presumed to be low was expected to improve psychiatric symptoms; thus, it may not be easy to conclude that increased doses are meaningless.

Based on the above, in case that the effect of an antipsychotic is insufficient with inadequate dose, it is advisable to consider increasing the dose.

This CQ is for acute phase of schizophrenia, and not treatment-resistant schizophrenia. However, it is assumed that a certain number of cases of poor drug responsiveness will result in a course of treatment resistance; therefore, it is necessary to consider the use of clozapine in such cases in the future. The Japanese criteria for clozapine use stipulate that the "sufficient dose" of antipsychotics is at least 600 mg/day of chlorpromazine equivalent,[8] and this CQ also uses this value as a guideline for dose increases (see CQ5-1 for definition of treatment resistance). However, it should be noted that rapid dose escalation and dose escalation exceeding the recommended dose not only lack evidence of efficacy, but may also exacerbate side effects.[9-11]

2. Whether to switch antipsychotics or continue at the current dose without switching

Leucht et al. conducted a systematic review of RCTs on whether to continue antipsychotics previously taken or switch to another.[12] Only an overview of 10 RCTs was provided (no meta-analysis was conducted). According to this review, none of the cases were limited to cases of first-episode psychosis, but no conclusions could be drawn

about the efficacy of switching to another antipsychotic. However, when looking at the individual RCTs, one suggested the effectiveness of switching, although the effect was slight. Kinon et al.[13] allocated cases for which 2–6 mg/day risperidone had an insufficient effect into a group that switched to 10–20 mg/day olanzapine ($n = 186$) and a group that continued the administration of 2–6 mg/day risperidone ($n = 192$). Follow-up observations were conducted for 10 weeks, and the results showed that there was a significant improvement in the PANSS total score in the olanzapine-switching group (range of improvement was 3.7 points higher in the switching group). Both groups exhibited discontinuation rates of approximately 30% with no significant difference, and there were no reports on adverse events or QOL issues.

Given these findings, although an improvement in symptoms is not necessarily expected by switching antipsychotics, the possibility of efficacy being demonstrated still exists.

Based on the above, it is advisable to consider switching antipsychotics in cases that the effect of the current antipsychotic is insufficient.

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CQ1-3: WHICH IS MORE APPROPRIATE, ANTIPSYCHOTIC MONOTHERAPY OR ANTIPSYCHOTIC COMBINATION THERAPY, IN CASE THAT ANTIPSYCHOTICS ARE INEFFICACIOUS IN ACUTE PHASE OF SCHIZOPHRENIA?

Recommendation

When antipsychotic monotherapy in acute phase of schizophrenia was inefficacious, no differences were observed with antipsychotic combination therapy when compared to cases without combination use in terms of the improvement in overall psychiatric symptoms (C), occurrence of all adverse events (excluding death) (C), discontinuation due to adverse events (B), all-cause discontinuation (B), and quality of life (QOL) improvement (D).

Based on these evidences, considering efficacy and safety, even if monotherapy in acute phase of schizophrenia is inefficacious, we suggest continuing monotherapy rather than initiating combination therapy (2C).

Commentary

Antipsychotic monotherapy should be initiated in acute phase of schizophrenia., But no or only a partial response is observed in a certain percentage of cases. In such cases, antipsychotic combination therapy is often accepted in daily clinical practice. In this CQ, we investigated the evidence underlying the findings through a meta-analysis of randomized controlled trials (RCTs).

Results showed that combination therapy improved overall psychiatric symptoms when monotherapy was ineffective (N [number of studies] = 29; n [number of patients] = 2398; risk ratio 0.73; 95% CI: 0.64–0.83, $p < 0.0001$), but we have to take care of interpreting the results.[1] Because, although the sensitivity analysis did not reveal any conflicting trend, 19 of the 29 RCTs allowed the use of clozapine or additional clozapine, which is not feasible in the Japanese setting, and only five RCTs[2–6] examined combination therapy, which is feasible in the Japanese setting. Furthermore, no significant differences were observed between the two groups in any of these studies. Therefore, it is believed that combination therapy is less likely to improve overall psychiatric symptoms compared with monotherapy in the Japanese setting (C).

For all-cause discontinuation, there was no significant difference between the combination therapy and monotherapy groups ($N = 43$, $n = 3137$, risk ratio 0.90, 95% CI: 0.76–1.07, $p = 0.24$)[1] (B).

For discontinuation due to adverse events, there was no significant difference between the both groups ($N = 18$, $n = 1611$, risk

ratio 0.84, 95% CI: 0.53–1.33, $p=0.455$), and publication bias was examined with the Egger test but not found (intercept = −0.57, 95% CI: −0.53–1.47, $p=0.20$).[7] However, 10 of 18 RCTs involved the use of clozapine or additional clozapine, and only four RCTs[2,3,6,8] investigated combination therapies that could be implemented in the Japanese setting. And no significant differences were observed between both groups in any of these studies (B). Additionally, the maximum observation period was 16 weeks (8 weeks or less for the majority), which was insufficient for evaluating adverse events. Thus, it would not be possible to conclude that combination therapy was effective for these outcomes.

For QOL, four RCTs ($n=389$) were reported,[6,9–11] but the QOL in each RCT assessed using different measures; no meta-analysis was conducted.[1] And no significant differences were observed in any of the RCTs. Additionally, of the four RCTs, three involved combination use with clozapine or additional clozapine, and only one RCT[6] investigated combination therapy that could be implemented in a Japanese setting. Furthermore, no significant differences were observed between the two groups in this study. Therefore, no differences were observed in QOL improvement (D). It is expected that RCTs will be conducted with standardized measures for QOL in the future.

For all adverse events, occurrence was significantly less with combination therapy ($N=22$; $n=1492$, risk ratio 0.77, 95% CI: 0.66–0.90, $p=0.001$), but Egger's test (intercept = −0.92, 95% CI: −1.80 – −0.04, $p=0.04$) showed publication bias.[7] Additionally, 10 out of 22 RCTs involved combination use with clozapine or additional clozapine, and only three RCTs examined combination that could be implemented in the Japanese setting.[3,8,12] There were no significant differences between the two groups in any of these studies (C). Additionally, the maximum observation period in many of these RCTs was 12 weeks, which is an insufficient period for evaluating adverse events. Therefore, it is not appropriate to apply these reports directly to the Japanese setting.

Based on these evidences, when efficacy and safety are considered, if monotherapy is inefficacious in acute-phase schizophrenia, we suggest continuing monotherapy rather than initiating combination therapy (2C).

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CQ1-4: WHICH IS MORE APPROPRIATE, ANTIPSYCHOTIC MONOTHERAPY OR CONCOMITANT THERAPY WITH PSYCHOTROPICS OTHER THAN ANTIPSYCHOTICS, IN CASE THAT ANTIPSYCHOTICS ARE INEFFICACIOUS IN ACUTE PHASE OF SCHIZOPHRENIA?

Recommendation

The concomitant use of psychotropics other than antipsychotics such as lithium, valproate, lamotrigine, and benzodiazepine receptor agonists with antipsychotic drugs did not differ from monotherapy with respect to improvement in overall psychiatric symptoms (D), all-cause discontinuation (C), discontinuation due to adverse events (C), or occurrence of adverse events (C).

Based on these evidences, considering efficacy and safety, even if antipsychotics are inefficacious in acute phase of schizophrenia, we suggest antipsychotic monotherapy rather than concomitant therapy with non-antipsychotics (2C).

Commentary

This CQ evaluates whether the concomitant use of psychotropics other than antipsychotics is appropriate, in case that no or only partial response to antipsychotic monotherapy in patients with schizophrenia. The psychotropics evaluated in this CQ were lithium,

valproate, lamotrigine, and benzodiazepine receptor agonists, which are often used concomitantly in psychiatric care, and other psychotropics were not considered.

Concomitant use of lithium was evaluated mainly based on data from a meta-analysis[1] in the Cochrane Database of Systematic Reviews. There was no clear improvement in psychiatric symptoms with concomitant use of lithium (D), no significant difference in all-cause discontinuation (C) and discontinuation due to adverse events (D), and no reports on quality of life (QOL). In general, the potential risk of side effects during long-term use of lithium needs to be considered. Based on the above, we suggest that concomitant use of lithium is not to be implemented for schizophrenia (2D).

Concomitant use of valproate was evaluated mainly based on data from a meta-analysis[2] in the Cochrane Database of Systematic Reviews. There was no clear improvement in psychiatric symptoms with the concomitant use of valproate (D), no significant difference in all-cause discontinuation (B), discontinuation due to adverse events (B), and adverse events (C). And there were no reliable reports regarding QOL. In general, the potential risk of side effects during long-term use of valproate needs to be considered. Based on the above, we suggest that concomitant use of valproate is not to be implemented for schizophrenia (2D).

Concomitant use of lamotrigine was evaluated based on data from a meta-analysis[3] in the Cochrane Database of Systematic Reviews. There was no improvement in psychiatric symptoms with concomitant use of lamotrigine (B), no increase in all-cause discontinuation (B) and a significant increase in all adverse events (C). However, there were no reports on whether discontinuation due to adverse events increased and no reliable reports regarding QOL. Based on the above, we suggest that concomitant use of lamotrigine is not to be implemented for schizophrenia (2B).

Concomitant use of benzodiazepine receptor agonists was evaluated mainly based on data from a meta-analysis.[4] There was no clear improvement in psychiatric symptoms with concomitant use of benzodiazepine receptor agonist (D), no significant difference in discontinuation due to adverse events (C), all-cause discontinuation (C), and all adverse events (C). And there were no reliable reports regarding QOL. Based on the above, we suggest that antipsychotics is not to be concomitantly used with benzodiazepine receptor agonists (2C). Please see Section CQ6-1 for details on the use of benzodiazepine receptor agonists for insomnia.

In this CQ, the concomitant use of the aforementioned four psychotropics was investigated, but it was not possible to recommend concomitant use for any of them. Considering that the concomitant use of any of these psychotropics for schizophrenia is off-label in the Japanese setting, careful consideration should be given to their use.

Based on these evidences, considering efficacy and safety, if the effect of antipsychotics is insufficient in acute phase of schizophrenia, we suggest that antipsychotic monotherapy be continued rather than initiating concomitant therapy with psychotropics other than antipsychotics (2C).

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CHAPTER 2: TREATMENT IN STABLE/MAINTENANCE PHASE OF SCHIZOPHRENIA

CQ2-1: IS DISCONTINUATION OF ANTIPSYCHOTICS RECOMMENDED FOR STABLE SCHIZOPHRENIA?

Recommendation

In cases of stable schizophrenia, when compared to the continuation of antipsychotics, the discontinuation of antipsychotics was associated with increase in relapse (A), increase in rehospitalization (A), increase in treatment discontinuation (A), worsening of psychiatric symptoms (A), and worsening of quality of life (QOL) (B). For adverse events, when compared to the continuation of antipsychotics, the discontinuation of antipsychotics was not associated with improvement in one or more adverse events (A), improvement in akathisia (A), improvement in muscle rigidity (B), and improvement in tremors (A) but was associated with increased occurrence of dyskinesia (A). Meanwhile, when compared to the continuation of antipsychotics, the discontinuation of antipsychotics resulted in decrease in the occurrence of dystonia (A), decrease in the occurrence of sedation (A), and decrease in the occurrence of weight gain (A).

Based on this evidence, when considering efficacy and safety, it is strongly recommended that antipsychotics be continued and not discontinued for cases with stable schizophrenia (1A).

Commentary

Many patients with stable schizophrenia wish to stop taking antipsychotics. If this could be done safely, then physicians can proceed with therapy that meets the patient's needs. This clinical issue is extremely important for both patients and physicians. The stages of schizophrenia are classified into acute, stabilization, and stable phases. Although there are no strict guidelines or algorithms that define these phases, the general consensus is that the acute phase is when symptoms are active and the patient's condition is unstable, the stabilization phase is when symptoms are improving and the patient's condition is stabilizing, and the stable phase is when symptoms disappear and the disease is stable.[1]

There is no strict definition of stable schizophrenia; thus, for this CQ, we utilized a more comprehensive meta-analysis[2] that included patients with schizophrenia who were thought to be stable (65 randomized controlled trials [RCTs], 6493 cases). According to these

results, the occurrence of "relapse" was significantly higher with discontinuation of antipsychotics than with continuation (N [number of studies] = 62, n [number of patients] = 6392, risk ratio 0.35, 95% CI: 0.29–0.41, $p < 0.00001$, continuation 22%, discontinuation 57%) (A). The occurrence of "rehospitalization" was also significantly higher with discontinuation of antipsychotics than with continuation ($N = 16$, $n = 2090$, risk ratio 0.38, 95% CI: 0.27–0.55, $p < 0.00001$, continuation 10%, discontinuation 26%) (A). The occurrence of "treatment discontinuation" was significantly higher with discontinuation of antipsychotics than with continuation ($N = 57$, $n = 4718$, risk ratio 0.53, 95% CI: 0.46–0.61, $p < 0.00001$, continuation 30%, discontinuation 54%) (A). The discontinuation of antipsychotics increased the occurrence of unimproved or worsened psychiatric symptoms ($N = 14$, $n = 1524$, risk factor 0.73, 95% CI: 0.64–0.84, $p < 0.00001$, continuation 70%, discontinuation 88%) (A). The discontinuation of antipsychotics also worsened the QOL ($N = 3$, $n = 527$, standardized mean difference = −0.62, 95% CI: −1.15 – 0.09, $p = 0.02$) (B).

For adverse events, there was no difference in improvement of at least one adverse event between the continuation and discontinuation of antipsychotics ($N = 10$, $n = 2184$) (A). Details of each adverse event are as follows. Compared with the continuation of antipsychotics, discontinuation was associated with increased occurrence of dyskinesia ($N = 13$, $n = 1820$, risk ratio 0.52, 95% CI: 0.28–0.97, $p = 0.04$) (A), reduced occurrence of dystonia ($N = 6$, $n = 824$, risk ratio 1.89, 95% CI: 1.05–3.41, $p = 0.04$) (A), reduced occurrence of sedation (N = 10, $n = 2146$, risk ratio 1.50, 95% CI: 1.22–1.84, $p = 0.0001$) (A), and reduced occurrence of weight gain (N = 10, $n = 2321$, risk ratio 2.07, 95% CI: 2.31–3.25, $p = 0.002$) (A). There was no difference in the occurrence of akathisia (A), muscle rigidity (B), or tremors (A) between the continuation and discontinuation of antipsychotics.

Based on this evidence, when considering efficacy and safety, it is strongly recommended that antipsychotics be continued and not discontinued for cases of stable schizophrenia (1A).

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CQ2-2: IS DOSE REDUCTION OF ANTIPSYCHOTICS RECOMMENDED FOR STABLE SCHIZOPHRENIA?

Recommendation

For stable schizophrenia, when compared to dose maintenance of antipsychotics, dose reduction of antipsychotics was associated with increase in relapse (A) but no differences were observed with regard to increase in rehospitalization (B), increase in treatment discontinuation (A), worsening of overall psychiatric symptoms (A), and improvement in quality of life (QOL) (B). No differences were also observed regarding improvement in extrapyramidal symptoms (B), weight loss (B), and negative symptoms (B), but dose reduction of antipsychotics improved cognitive function (C).

Based on this evidence, when considering efficacy and safety, it is weakly recommended that the dose of antipsychotics be maintained rather than reduced for stable schizophrenia (2A).

If the dose after the reduction exceeded 200 mg/day of chlorpromazine dose equivalents, there was no difference in relapse between the dose reduction and dose maintenance. Thus, if the dose after the reduction exceeds 200 mg/day of chlorpromazine dose equivalents, dose reduction may be worth trying.

Commentary

Antipsychotics play a central role in the treatment of symptoms of schizophrenia, especially positive symptoms such as hallucinations, delusions, and disorganization. The continuation of antipsychotics is required to prevent relapse not only in the acute phase when positive symptoms are active but also in the maintenance phase after these symptoms have stabilized[1] (see CQ2-1 for details). However, antipsychotics can cause various side effects such as extrapyramidal symptoms, hyperprolactinemia, metabolic disorders, and cardiovascular disorders. Regardless of whether first- or second-generation antipsychotics are used, increased doses increase the risk of extrapyramidal symptoms,[2] sudden cardiac death,[3] venous thrombosis,[4] myocardial infarction,[5] and antipsychotic-induced cognitive decline.[6-8] Considering these dose-dependent side effects, it is believed that antipsychotics should be administered at the minimum necessary dose. Additionally, it is natural for patients and their families to want to reduce the dose of antipsychotics after psychiatric symptoms in the acute phase have stabilized. Therefore, in cases with stable schizophrenia, it is desirable to examine the necessity of continuing the required dose in the acute phase and whether dose reduction is possible.

As a result of a systematic literature search, we utilized a meta-analysis of randomized controlled trials (RCTs) that compared dose reduction and dose maintenance of antipsychotics (N [number of studies] = 18, n [number of patients] = 1385).[9] Compared with dose maintenance of antipsychotics, dose reduction was associated with a significantly higher occurrence of relapse ($N = 13$, $n = 902$, risk ratio 1.96, 95% CI: 1.23–3.12, $p = 0.005$) (A). Meanwhile, there were no significant differences with regard to increases in rehospitalization (B), increases in treatment discontinuation (A), worsening of overall psychiatric symptoms (B), therapy interruption due to adverse events (A), improvements in extrapyramidal symptoms (B), weight loss (B), improvements in negative symptoms (B), and improvements in QOL (B). When compared to dose maintenance of antipsychotics, dose reduction was associated with significant improvements in cognitive function ($N = 2$, $n = 136$, standardized mean difference = 0.69, 95% CI: 0.25–1.12, $p = 0.002$) (C). Therefore, dose reduction of antipsychotics increases the risk of relapse, and regarding adverse events, only a small number of RCTs have shown improvements in cognitive function.

Based on this evidence, when considering efficacy and safety, it is weakly recommended that the dose of antipsychotics be maintained rather than reduced for stable schizophrenia (2A).

In subgroup analysis to compare the groups with the doses after dose reduction of ≤200 and > 200 mg/day of chlorpromazine dose

equivalents, there was no significant difference in relapse if the dose after dose reduction was >200 mg/day ($N = 7$, $n = 345$, risk ratio 1.07, 95% CI: 0.57–2.02, $p = 0.83$).[9] In other words, if the dose after the reduction exceeds 200 mg/day of chlorpromazine dose equivalents, dose reduction is worth trying. Although this conclusion was regarded as a semi-recommendation in the process of creating this guideline, it was ultimately included as a recommendation after repeated discussions among the guideline development members, including patients and their families.

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CQ2-3: ARE EXTENDED DOSING AND TARGETED/INTERMITTENT DOSING OF ANTIPSYCHOTICS RECOMMENDED FOR STABLE SCHIZOPHRENIA?

Recommendation

In stable schizophrenia, compared with continuous administration of antipsychotics, extended dosing and targeted/intermittent dosing was associated with increased relapse (A), increase in rehospitalization (A), and increase in treatment discontinuation (C), but there were no differences with regard to worsening of psychiatric symptoms (B) and improvement in quality of life (QOL) (C). Meanwhile, compared with continuous administration of antipsychotics, extended dosing and targeted/intermittent dosing were associated with decrease in the occurrence of extrapyramidal symptoms (C), but there were no differences regarding the occurrence of side effects requiring additional medication (C) and the occurrence of tardive dyskinesia (B).

Based on this evidence, when considering efficacy and safety, it is weakly recommended that continuous administration rather than extended dosing and targeted/intermittent dosing be given for cases of stable schizophrenia (2A).

Commentary

In treatment with antipsychotics for schizophrenia, it is common to take drugs daily, but patients who are stable may want to reduce this frequency. There are other administration methods such as extended dosing, in which the dosing is regular, but the interval is lengthened more than usual, and a targeted/intermittent dosing, in which drug administration is ceased until relapse of psychotic symptoms is suspected. In this CQ, we investigated stable schizophrenia defined according to CQ2-1.

A meta-analysis by De Hert et al.[1] of randomized controlled trials (RCTs) that compared intermittent and continuous administration of antipsychotics in stable schizophrenia showed that intermittent administration had a significantly more relapse than continuous administration (N [number of studies] = 10, n [number of patients] = 1230, odds ratio 3.36, 95% CI: 2.36–5.45, $p < 0.0001$) (A). This finding was similar for patients with first-episode psychosis and those with multi-episode psychosis. In the observation period of ≥26 weeks in the meta-analysis by Sampson et al.,[2] which was the longest observation period among the studies, patients with extended dosing and targeted/intermittent dosing had significantly more relapse than those with continuous administration ($N = 7$, $n = 436$, risk ratio 2.46, 95% CI: 1.70–3.54, $p < 0.00001$). Rehospitalization was significantly greater with extended dosing and targeted/intermittent dosing than with continuous administration ($N = 5$, $n = 626$, risk ratio 1.65, 95% CI: 1.33–2.06, $p < 0.00001$)[2] (A). Extended dosing and targeted/intermittent dosing significantly increased treatment discontinuation compared with that by continuous administration ($N = 10$, $n = 996$, risk ratio 1.63, 95% CI: 1.23–2.15, $p = 0.00064$) (C), but there was no significant difference from continuous administration in worsening of psychiatric symptoms (B) and improvement in QOL (C).[2]

For adverse events, compared with continuous administration, extended dosing and targeted/intermittent dosing significantly reduced the occurrence of parkinsonism ($N = 1$, $n = 43$, risk ratio 0.13, 95% CI: 0.02–0.96, $p = 0.045$), but there was only one RCT included[2] (C). There were no significant differences between the two groups in the occurrence of side effects requiring additional medication (C) or the occurrence of tardive dyskinesia (B).

These results indicate that, compared with continuous administration of antipsychotics, extended dosing and targeted/intermittent dosing increased relapse and rehospitalization. Although the occurrence of extrapyramidal symptoms decreased with extended dosing and targeted/intermittent dosing, no difference was observed between the two groups in the occurrence of side effects requiring additional medication or the occurrence of tardive dyskinesia.

Based on this evidence, when considering efficacy and safety, it is weakly recommended that continuous administration rather than

extended dosing and targeted/intermittent dosing is given for cases of stable schizophrenia (2A).

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CQ2-4: WHICH FIRST-GENERATION ANTIPSYCHOTICS OR SECOND-GENERATION ANTIPSYCHOTICS IS MORE USEFUL IN MAINTENANCE PHASE OF SCHIZOPHRENIA?

Semi-recommendation

For treatment in maintenance phase of schizophrenia, second-generation antipsychotics (SGAs) had fewer relapses and rehospitalizations than first-generation antipsychotics (FGAs). However, there were no differences in all-cause treatment discontinuation. Additionally, compared with FGAs, SGAs were associated with less tardive dyskinesia in patients with schizophrenia undergoing long-term use of antipsychotics.

From the above, it is desirable to use SGAs rather than FGAs for treatment in maintenance phase of schizophrenia.

Commentary

Repeated relapses are known to worsen psychotic symptoms and decline social functioning. Therefore, relapse prevention is one of the most important issues for treatment in maintenance phase of schizophrenia. The illness phase of schizophrenia is classified into acute, stabilization, and stable phases. Although there are no strict guidelines or algorithms that define these phases, the general consensus is that the acute phase is when symptoms are active and the condition is unstable, the stabilization phase is when symptoms are improving and the condition is stabilizing, and the stable phase is when symptoms disappear and the condition is stable.[1] There are many cases where the stabilization and stable phases are combined and defined as the maintenance phase, and this CQ describes treatment during this maintenance phase.

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but a sufficient body of evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved using a manual search, such as that obtained from observational studies. Kishimoto et al. reported a meta-analysis that compared the preventive effects of FGAs and SGAs on relapse during the maintenance phase of schizophrenia (N [number of studies] = 23, n [number of patients] = 4504).[2] The inclusion criteria for this meta-analysis were studies that directly compared FGAs and SGAs with a follow-up period of at least 6 months (mean duration: 61.9 ± 22.4 weeks). The breakdown of the number of trials for each antipsychotic included in the meta-analysis was as follows: (1) for SGAs, amisulpride, three trials; aripiprazole, two trials; clozapine, four trials; iloperidone, three trials; olanzapine, six trials; quetiapine, one trial; risperidone, six trials; sertindole, one trial; and ziprasidone, one trial; (2) for FGAs, haloperidol, 21 out of 23 trials. The cases with SGAs had significantly fewer relapses than those with FGAs, but the former was slightly superior than the letter (SGA relapse rate = 29.0%, FGA relapse rate = 37.5%, risk ratio = 0.80, number needed to treat = 17, $p = 0.0007$). Similarly, cases with SGAs had significantly fewer rehospitalizations than those with FGAs (risk ratio = 0.72, $p = 0.004$). Meanwhile, cases with SGAs tended to have fewer all-cause treatment discontinuation than those with FGAs, but there was no significant difference (risk ratio = 0.90, $p = 0.06$).

Tardive dyskinesia is an involuntary movement that occurs with long-term use of antipsychotics and may be irreversible once established. Carbon et al. reported a meta-analysis ($N = 32$, $n = 10\,706$) that compared the risk of the occurrence of tardive dyskinesia between FGAs and SGAs.[3] Patients with schizophrenia using antipsychotics were included regardless of whether they were in the maintenance phase, provided the illness duration was 14 years for SGA cases and 13.7 years for FGA cases, and these patients can be regarded as having used antipsychotics for a relatively long time. According to these results, cases with SGAs had a significantly lower occurrence of tardive dyskinesia than those with FGAs (SGA occurrence rate = 2.6%, FGA occurrence rate = 6.5%, risk ratio = 0.47, number needed to treat = 20, $p < 0.0001$).

Improvements in quality of life (QOL) and mortality are important outcomes, but no clear evidence on them was found.

Based on the above, it is desirable to use SGAs rather than FGAs in maintenance phase of schizophrenia.

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CQ2-5: ARE LONG-ACTING INJECTIONS OF ANTIPSYCHOTICS USEFUL IN MAINTENANCE PHASE OF SCHIZOPHRENIA?

Semi-recommendation

In studies where the enrolled patients were believed to be adherent, treatment with long-acting injections (LAIs) did not differ from that with oral drugs in terms of relapse rate, treatment discontinuation due to adverse events, and mortality. Meanwhile, in studies under conditions close to those in actual clinical practice, where medication adherence is not guaranteed, compared with oral drugs, LAIs were associated with fewer rehospitalization, all-cause treatment

discontinuation, and mortality. Based on the above reports, it is desirable to use LAIs in maintenance phase of schizophrenia in cases where relapse due to decrease in medication adherence is a problem. Additionally, it is desirable to use LAIs if the patient wishes.

Commentary

In actual clinical practice, the problem of decreased medication adherence can occur with many patients, but medical professionals should not treat this as "bad behavior," instead understand that in the first place, medication adherence tends to worsen easily. LAIs are a formulation designed to maintain constant blood concentrations of antipsychotics to overcome this problem, with maximum efficacy in circumstances where there is low medication adherence.[1] In fact, results of a meta-analysis that compared LAIs and oral drugs differed between research designs based on randomized controlled trials (RCTs) with a high level of evidence and those based on observational studies with a low level of evidence that set conditions more consistent with clinical practice.[2] Because in this guideline, the observational study designs had a low level of evidence, our conclusion did not reach the level of a recommendation, instead remained a semi-recommendation.

For the relapse rate, a meta-analysis of RCTs (N [number of studies] = 21, n [number of patients] = 5176) showed no significant difference in the preventive effects of LAIs and oral drugs on relapse.[3] However, no evaluations of observational studies had been conducted.

For hospitalization, the above-mentioned meta-analysis of the RCTs did not show a significant difference between LAIs and oral drugs.[3] However, a meta-analysis of mirror-image studies (N = 25, n = 5940) showed that, although there was considerable inter-study variability, LAIs were significantly different compared with oral drugs in terms of the prevention of hospitalization (N = 16, n = 4066, risk ratio 0.43, 95% CI: 0.35–0.53, p < 0.001; heterogeneity: τ^2 = 0.117, I^2 = 87.6%, Q = 121, df = 15, p < 0.001) and decrease in number of hospitalizations (N = 15, 6342 person-years [calculated as the number of hospitalizations divided by the number of years at risk], risk ratio 0.38, 95% CI: 0.28–0.51, p < 0.001; heterogeneity: τ^2 = 0.301, I^2 = 95.0%, Q = 280, df = 14, p < 0.001).[4] A meta-analysis of cohort studies (N = 42, n = 101 624) also showed that, although there was significant inter-study heterogeneity, LAIs were significantly different compared with oral drugs in terms of hospitalization rate (N = 15, 68 009 person-years, risk ratio 0.85, 95% CI: 0.78–0.93, p < 0.001; number needed to treat = 6, 95% CI: 4–17; heterogeneity: τ^2 = 0.02, I^2 = 94.9%, Q = 272.6, df = 14, p < 0.001).[5]

For all-cause treatment discontinuation, the above-mentioned meta-analysis of RCTs did not show a significant difference between LAIs and oral drugs,[3] but the above-mentioned meta-analysis of cohort studies showed that LAIs were significantly different from oral drugs (N = 10, n = 37 293, risk ratio 0.78, 95% CI: 0.67–0.91, p = 0.001; heterogeneity: τ^2 = 0.04, I^2 = 93.0%, Q = 128.6, df = 9, p < 0.001).[5] For treatment discontinuation due to adverse events, the above-mentioned meta-analysis of RCTs did not show a significant difference between LAIs and oral drugs,[3] and no evaluation of observational studies was conducted. A meta-analysis based on RCTs (N = 52, n = 17 416) did not show any significant differences in mortality between LAIs and oral drugs.[6] Additionally, research that was based on data collected in Sweden (n = 29 823) evaluating the association between all-cause mortality and each drug, including LAIs (evaluation period: mean = 5.7 years, median = 6.9 years), showed that the lowest cumulative mortality was observed with cases of LAI using second-generation antipsychotics (SGAs) (maximum follow-up period = 7.5 years; mortality with SGA LAIs = 7.5%, oral SGAs = 8.5%, oral first-generation antipsychotics [FGAs] = 12.2%, FGA LAIs = 12.3%, and not using antipsychotics = 15.2%], and the mortality risk in all cases using LAIs (hazard ratio 0.67, 95% CI: 0.56–0.80, p < 0.0001) was significantly lower than that in all cases using oral drugs.[7] When using LAIs, it is necessary to pay attention to the precautions described in the package insert and use the drug appropriately.

A meta-analysis on the impact of LAI use on the quality of life (QOL)[8] showed that two RCTs[9,10] identified significant changes in mean QOL, but different evaluation scales were used in each trial, and thus the data could not be integrated. Additionally, there is a study, pointing out that insufficient knowledge is currently available to guide the selection of specific LAIs, given differences in the association between clinical symptoms and functional evaluations among SGA LAIs.[11]

LAIs are more expensive than oral drugs, but they have been reported to be cost-effective.[12] However, sufficiently reliable research is still lacking, and future research is needed. Additionally, if the patient wishes to be treated with an LAI, that option should be considered; however, it is preferred that LAIs be introduced after the patient has been educated to some extent on it and careful explanations are provided by the medical personnel.

Based on the above, for treatment in maintenance phase of schizophrenia, it is desirable to use LAIs in cases where relapse is a problem due to decreased medication adherence. An LAI can also be used if the patient wishes.

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CHAPTER 3: EXTRAPYRAMIDAL SIDE EFFECTS OF ANTIPSYCHOTICS

CQ3-1: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR PARKINSONISM DUE TO ANTIPSYCHOTICS?

Semi-recommendation

When drug-induced parkinsonism occurs, then as a rule, the dose of the causative drug should be reduced, and in severe cases, the drug should be temporarily discontinued and another antipsychotic should be administered. If the causative drug is effective for psychiatric symptoms, then the advantages and disadvantages of its dose reduction or discontinuation should be carefully considered. When changing antipsychotics, then those with a low risk of parkinsonism, such as second-generation antipsychotics (SGAs), are preferred. If the addition of anticholinergics is necessary, then attention should be paid to their side effects.

It is preferable to select SGAs over first-generation antipsychotics (FGAs) as a preventive method for drug-induced parkinsonism.

Commentary

Drug-induced parkinsonism occurs within a few weeks after drug administration. It tends to occur after middle age, and in many cases, the risk of onset increases depending on the antipsychotic dose, but the onset is also affected by individual vulnerabilities such as the presence of organic brain diseases and aging.[1] Similar to idiopathic parkinsonism, muscle rigidity, bradykinesia, dysarthria, dysphagia, and postural dysregulation are observed in drug-induced parkinsonism; however, in the latter, bilateral symptoms are common, and resting tremors may not be seen.[2] Drug-induced parkinsonism interferes with a patient's behavior; causes inactivity, falls, aspiration, etc.; and is a risk factor for tardive dyskinesia, and it is important to address these symptoms.[3]

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but the sufficient body of evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies. As with other drug-induced side effects, when antipsychotic side effects occur, the general principles are to reduce the dose of the causative drug, temporarily discontinue it in severe cases, and carefully consider the advantages and disadvantages of dose reduction and discontinuation. A few high-quality studies have been conducted but with no conclusive results. Nevertheless, the lack of substantial results does not constitute a basis for disregarding the self-evident nature of this action. We describe the general principles for drug-induced parkinsonism first, followed by therapies to consider when addressing these general principles is difficult.

For drug-induced parkinsonism due to antipsychotics, there was insufficient evidence regarding changing individual drugs. The "Maudsley Prescribing Guidelines in Psychiatry 13th Edition"[4] and the World Federation of Societies of Biological Psychiatry (WFSBP) guideline[5] state that the risk of drug-induced parkinsonism is high for many FGAs and low for SGAs. Therefore, when changing antipsychotics, those with a low risk of parkinsonism, such as SGAs, are desirable.

Among RCTs on the addition of other therapies for drug-induced parkinsonism due to antipsychotics, there are reports on the addition of biperiden and amantadine[6] and also on the addition of clonazepam.[7] The quality of evidence in these studies was low, and no conclusions could be drawn. However, pharmacological therapies for schizophrenia (antipsychotics) often cause drug-induced parkinsonism, so clinicians are currently treating patients based on consensus guidelines or experience rather than RCT evidence.[8,9] Regarding therapies for drug-induced parkinsonism, several guidelines and reviews have specified antipsychotic dose reductions, changing to antipsychotics with a low risk of parkinsonism such as SGAs, addition of anticholinergics,[4,5,10–13] or addition of dopamine agonists.[5,10–13] When adding anticholinergics or dopamine agonists, the former may cause anticholinergic side effects, and the latter may exacerbate psychosis; thus, it has been recommended that excessive dosing and chronic use of these drugs should be avoided or minimized.[5,11]

For the selection of antipsychotics for the prevention of drug-induced parkinsonism, drugs with a low risk of occurrence are considered desirable. As described above, SGAs are known to have a lower risk than FGAs and are preferred. Sufficient evidence has not been obtained from comparative studies on the risks of individual drugs, so this guideline presents frequency information from Japanese clinical research.[14] Quantitative ranking is difficult, and this should be considered as a framework for clinical reference. Haloperidol was the most prominent drug that induced parkinsonism, with tremor in approximately 40%; bradykinesia in approximately 30%; and gait

abnormalities, musculoskeletal stiffness, and excessive salivation in approximately 25% of cases. For SGAs, the occurrence of tremors was relatively high at approximately 20% for blonanserin and risperidone, approximately 15% for perospirone, and approximately 10% for olanzapine and aripiprazole. Meanwhile, the occurrence of muscle rigidity and musculoskeletal stiffness was relatively high at approximately 10% for risperidone, perospirone, and blonanserin, and the occurrence of gait abnormalities and difficulty walking was relatively high at approximately 15% for risperidone.

For the prevention of drug-induced parkinsonism, there was a trial that used trihexyphenidyl in combination with an antipsychotic, but sufficient evidence was not obtained. The International College of Neuropsychopharmacology (CINP) guideline states that prophylactic anticholinergics should be considered only for high-risk cases of antipsychotic use since anticholinergics also have side effects, and prophylactic anticholinergics should be downtitrated or discontinued after the implementation of treatment.[10]

It is preferable to select SGAs over FGAs as a preventive method for drug-induced parkinsonism.

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CQ3-2: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR ACUTE DYSTONIA DUE TO ANTIPSYCHOTICS?

Semi-recommendation

When acute dystonia occurs, then as a rule, the causative drug dose should be reduced, and in severe cases, the drug should be temporarily discontinued and another antipsychotic should be administered. If the causative drug is effective for psychiatric symptoms, then the advantages and disadvantages of its dose reduction or discontinuation should be carefully considered.

When changing antipsychotics, it is desirable to switch to those with a low risk of acute dystonia, such as second-generation antipsychotics (SGAs) first. Next, oral or intramuscular administration of anticholinergics (biperiden and trihexyphenidyl) or an antihistamine (promethazine) should be considered after considering the anticholinergic side effects.

SGAs should be selected over first-generation antipsychotics (FGAs) as a preventive method for acute dystonia.

Commentary

Acute dystonia is common in young males and is characterized by abnormal posture and muscle stiffness due to involuntary and continuous muscle contractions that usually occur within 3 days after administration of antipsychotics. Elevation of the eyeballs and torsion of the neck and trunk are common, but they may be accompanied by pain; although rare, laryngeal dystonia can be life-threatening.[1,2] Approximately 80% of incidents occur from the afternoon to night. This may also be a factor in refusal to take medication.

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies. As with other drug-induced side effects, it is generally self-evident when antipsychotic side effects occur to reduce the dose of the causative drug, temporarily discontinue it in severe cases, carefully consider the advantages and disadvantages of dose reduction or discontinuation when administering other antipsychotics, and carefully consider if the causative drug is effective for psychiatric symptoms. A few high-quality studies have been conducted but with no conclusive results. Nevertheless, the lack of substantial results does not constitute a basis for disregarding the self-evident nature of this action. Thus, the general principles for acute dystonia are described below first,

after which we describe therapies to consider when it is difficult to address the general principles.

When changing the antipsychotic because of acute dystonia, using a drug with low risk of occurrence is desirable. As detailed in the prevention section, SGAs are known to have a lower risk than FGAs and are preferred. Sufficient evidence has not been obtained from comparative studies on the risks of individual drugs, so this guideline presents frequency information from Japanese clinical research.[3] Quantitative ranking is difficult, and this should be understood as a framework for clinical reference. Many clinical trials have indicated both acute and tardive dystonia, but the occurrence of dystonia in patients treated with SGAs was approximately 0.3%–6%, which was lower than the 12% value in patients treated with haloperidol. Next, oral or intramuscular administration of anticholinergics (biperiden and trihexyphenidyl) or an antihistamine (promethazine) was clinically used for the treatment of acute dystonia, and their use is presented in major guidelines.[4-7]

Regarding the choice of antipsychotic for the prevention of acute dystonia, a meta-analysis showed that aripiprazole (risk ratio 6.63, 95% CI: 1.52–28.86, $p=0.012$) and olanzapine (risk ratio 12.92, 95% CI: 1.67–99.78, $p=0.014$) significantly reduced the occurrence of acute dystonia.[8] Additionally, a meta-analysis showed that patients treated with quetiapine were significantly less likely to develop acute dystonia than those treated with FGAs (risk ratio 0.19, 95% CI: 0.06–0.64, $p=0.0072$).[9] In an observational study, a retrospective cohort of 1975 patients in the United States from 1997 to 2006 showed a significantly lower occurrence of acute dystonia in the SGA monotherapy group than in the FGA monotherapy group (odds ratio 0.12, 95% CI: 0.08–0.19).[10] Additionally, a prospective cohort study of 1337 patients who were admitted to a psychiatric emergency unit investigated the occurrence of acute dystonia that was associated with SGAs and FGAs, with SGAs showing a significantly lower occurrence ($p=0.000$).[11] Therefore, SGAs are preferable to FGAs as prophylactic antipsychotics.

Major international guidelines do not recommend prophylactic administration of antipsychotics for all patients and antipsychotic use is determined according to the risk factors for acute dystonia in each case (e.g., history of dystonia, use of FGAs, and being a young male).[5,6,12,13] Although there are studies on the effectiveness of prophylactic anticholinergics,[14,15] it is recommended that, when concomitantly using anticholinergics with antipsychotics, the former be used temporarily for several weeks after the start of therapy only if absolutely necessary.[16]

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CQ3-3: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR AKATHISIA DUE TO ANTIPSYCHOTICS?

Semi-recommendation

When akathisia occurs, then as a rule, the causative drug dose should be reduced, and in severe cases, the drug should be temporarily discontinued and another antipsychotic should be administered. In cases of high urgency, such as suicidal ideation, suicide attempts, and risk of harm to others, which are accompanied by intense anxiety and agitation, the active interventions such as psychotherapy and environmental adjustment should be conducted in addition to pharmacological therapy. If the causative drug is effective for psychiatric symptoms, then the advantages and disadvantages of its dose reduction or discontinuation should be carefully considered. If the antipsychotic dose reduction is ineffective, then switching to second-generation antipsychotics (SGAs) at the lowest possible dose is desirable.

SGAs should be selected over first-generation antipsychotics (FGAs) as a preventive method for akathisia.

Commentary

Akathisia is a side effect that is characterized by physical restlessness such as "fidgety movements of the lower limbs," "stepping," and "inability to sit still;" in mild cases, the patient can control the movements. Akathisia can also lead to suicidal ideation, suicide attempts, and harm to others, which are accompanied by strong feelings of anxiety and agitation. In such cases of high urgency, it is desirable to actively intervene, including the use of pharmacological therapy, psychotherapy, and environmental adjustments, including hospitalization. In this CQ, we investigate therapies and prevention methods for akathisia.

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies. As with other drug-induced side effects, it is generally self-evident when antipsychotic side effects occur to reduce the dose of the causative drug, temporarily discontinue it in severe cases, carefully consider the advantages and disadvantages of dose reduction or discontinuation when administering other antipsychotics, and carefully consider if the causative drug is effective for psychiatric symptoms. A few high-quality studies have been conducted but with no conclusive results. Nevertheless, the lack of substantial results does not constitute a basis for disregarding the self-evident nature of this action. The general principles for akathisia are described below first, after which we describe therapies to consider when addressing the general principles is difficult.

In other words, when akathisia occurs, as a rule, the dose of the causative drug should be reduced, and in severe cases, the drug should be temporarily discontinued and another antipsychotic administered. It is known from representative reviews and guidelines in other countries that the occurrence of akathisia is more dose-dependent if the causative drug is effective for psychiatric symptoms and the akathisia is mild.[1,2] Therefore, after a thorough discussion with the patient, the dose of the administered antipsychotic should be considered first.[2,3] If antipsychotic dose reduction is ineffective or inappropriate, then it is desirable to switch to the lowest possible dose of an SGA. This switching is because guidelines in other countries indicate that the risk of akathisia occurrence is low with SGAs.[2-4] The latest network meta-analysis on the risk of akathisia occurrence due to antipsychotics[5] indicated that all FGAs had a moderate relative risk compared with that of placebo. Among the SGAs marketed in Japan, risperidone, asenapine, aripiprazole, and brexpiprazole have low relative risks, and clozapine, olanzapine, quetiapine, and paliperidone have very low relative risks. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which was a large-scale, double-blind RCT targeting chronic-phase schizophrenia, there was no significant difference in the risk of occurring akathisia between the FGA perphenazine and the SGAs risperidone, olanzapine, and quetiapine.[6]

Although there are studies on other therapeutic interventions, the quality of evidence is very low, and only when the above measures are difficult or ineffective, the other therapeutic interventions considered for the first time. In Japan, the additional administration of anticholinergics has been used to treat akathisia, but this is not recommended because a systematic review by the *Cochrane Database of Systematic Reviews* in 2006 concluded that there were no studies demonstrating efficacy.[7] There are additional systematic reviews and RCTs regarding concomitant therapy with benzodiazepine receptor agonists,[8,9] β-blockers,[10] and agents with 5-HT_{2A} receptor antagonistic activity (mirtazapine, mianserin, and trazodone),[11] and some guidelines list these therapies as an option that may be considered.[2-4] However, when considering the small and imprecise nature of these studies, various unknown bias risks, low quality of evidence, direct side effects of these drugs, and possible interactions with antipsychotics, these therapies are not recommended; however, they are options to be considered depending on the patient's wishes when changing or reducing the antipsychotic dose is ineffective or difficult.

Regarding the selection of antipsychotic drugs for the prevention of akathisia, it is desirable to use drugs with a low risk of akathisia occurrence. As described above, SGAs are known to have a lower risk than FGAs and are preferred. Meanwhile, sufficient evidence has not been obtained from comparative studies on the risks of individual drugs, so this guideline presents frequency information from Japanese clinical research.[12] Quantitative ranking is difficult, and this should be understood as a framework for clinical reference. The frequency of occurrence of akathisia is low with SGAs (approximately 4%–25% compared with that of approximately 40% with haloperidol); among SGAs, perospirone and blonanserin have relatively high values at approximately 25%. Based on the above reports, using SGAs for the prevention of akathisia is preferable.

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CQ3-4: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR TARDIVE DYSKINESIA DUE TO ANTIPSYCHOTICS?

Semi-recommendation

When tardive dyskinesia occurs, then as a rule, the dose of the causative drug should be reduced, and in severe cases, the drug should be temporarily discontinued and another antipsychotic should be administered. If the causative drug is effective for psychiatric symptoms, then the advantages and disadvantages of its dose reduction or discontinuation should be carefully considered. When changing antipsychotics, switching to second-generation antipsychotics (SGAs) should be considered.

SGAs should be selected over first-generation antipsychotics (FGAs) as a preventive method for tardive dyskinesia.

Commentary

Tardive dyskinesia often refers to various involuntary movements of the neck, face, and mouth (e.g., pursed lip, tongue movement, and lip movement), as well as irregular movements of the upper and lower limbs that occur several months after taking antipsychotic drugs. Tardive dyskinesia can be irreversible, and no therapy has been established for this condition. In this CQ, we investigate therapy and prevention methods for tardive dyskinesia.

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies. As with other drug-induced side effects, it is generally self-evident when antipsychotic side effects occur to reduce the dose of the causative drug, temporarily discontinue it in severe cases, carefully consider the advantages and disadvantages of dose reduction or discontinuation when administering other antipsychotics, and carefully consider if the causative drug is effective for psychiatric symptoms. A few high-quality studies have been conducted but with no conclusive results. Nevertheless, the lack of substantial results does not constitute a basis for disregarding the self-evident nature of this action. The general principles for tardive dyskinesia, which can become irreversible upon onset, are described first, after which we describe therapies to consider when addressing these general principles is difficult.

There are no high-quality research reports on dose reductions, discontinuation, or changes in antipsychotics for tardive dyskinesia,[1,2] but guidelines and reviews from other countries have mentioned antipsychotic dose reduction and switching to SGAs as options.[3-8] Although there are studies on other therapeutic interventions, the quality of evidence is very low, and only when the above measures are difficult or ineffective, other therapeutic interventions considered for the first time. Systematic reviews that examined the efficacy of anticholinergics,[9] GABA agonists,[10] vitamin E,[11] calcium channel blockers,[12] cholinergics,[13] and benzodiazepine receptor agonists[14] for tardive dyskinesia were published in the *Cochrane Database of Systematic Reviews* in 2018, but the efficacy of these treatments was poor, and they are not recommended. There are also systematic reviews of concomitant therapies with vitamin B_6[15] and *Ginkgo biloba* extract[6,16]; however, the trials were small and imprecise, there were various unknown bias risks, and the quality of evidence was low, so they were not recommended. Nonetheless, they are options to be considered depending on the patient's wishes when changing or reducing the antipsychotic dose is ineffective or difficult.

Regarding the selection of antipsychotics for the prevention of tardive dyskinesia, drugs with a low risk of occurrence are considered desirable. Carbon et al.[17] conducted a meta-analysis of 11493 patients with tardive dyskinesia in 41 reports published between 2000 and 2015. The results showed that the prevalence of mild or severe tardive dyskinesia was significantly lower in the SGA therapy group (20.7%, 95% CI: 16.6%–25.4%) than in the FGA therapy group (30.0%, 95% CI: 26.4%–33.8%) ($p=0.002$). Within the SGA group, patients without previous FGA exposure had a particularly low prevalence (7.2%, 95% CI: 3.4%–14.5%). In another meta-analysis, Carbon et al. calculated the one-year occurrence of tardive dyskinesia and showed values of 6.5% (95% CI: 5.3%–7.8%) for FGAs as opposed to 2.6% (95% CI: 2.0%–3.1%) for SGAs.[18] Thus, the risk of SGAs was lower than that of FGAs, and SGAs were preferable to FGAs for the prevention of tardive dyskinesia, which is an assertion that is also supported by guidelines in other countries.[4,7,8] Meanwhile, sufficient evidence has not been obtained from comparative studies on the risks of individual drugs, so this guideline presents frequency information from Japanese clinical research.[19] Quantitative ranking is difficult, and this should be understood as a framework for clinical reference. The occurrence of tardive dyskinesia for SGAs was 0.6%–5.4%, which was lower than the value for haloperidol (7.6%). Based on the above, it is desirable to select SGAs over FGAs as a prevention method.

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CQ3-5: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR TARDIVE DYSTONIA DUE TO ANTIPSYCHOTICS?

Semi-recommendation

When tardive dystonia occurs, then as a rule, the dose of the causative drug should be reduced, and in severe cases, the drug should be temporarily discontinued and another antipsychotic should be administered. If the causative drug is effective for psychiatric symptoms, then the advantages and disadvantages of its dose reduction or discontinuation should be carefully considered. There is no established therapy for tardive dystonia, but switching to clozapine should be considered for treatment-resistant schizophrenia cases. Botulinum toxin may also be an effective therapy for focal dystonia. There is almost no evidence at this stage for the prevention methods, so we will not provide a response for specific drugs.

Commentary

Tardive dystonia refers to posture and movement abnormalities due to persistent and involuntary muscle tone that can occur several months after taking antipsychotics. In some patients, it becomes impossible to maintain posture and move smoothly, and this can lead to major difficulties in daily living activities, including walking.

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies. As with other drug-induced side effects, it is generally self-evident when antipsychotic side effects occur to reduce the dose of the causative drug, temporarily discontinue it in severe cases, carefully consider the advantages and disadvantages of dose reduction and discontinuation when administering other antipsychotics, and carefully consider if the causative drug is effective for psychiatric symptoms. A few high-quality studies have been conducted but with no conclusive results. Nevertheless, the lack of substantial results does not constitute a basis for disregarding the self-evident nature of this action. The general principles for tardive dystonia are described first, after which we describe therapies to consider when it is difficult to address these general principles. Regarding therapies and prevention methods for tardive dystonia, we examined antipsychotic dose reduction, antipsychotic dose maintenance, changes in antipsychotic, and antipsychotic drug continuation, but no clear data were available. We also examined major international guidelines that were referenced in the narrative review as well as late-onset syndrome guidelines by the American Academy of Neurology (AAN), but no recommended therapy or prevention methods were presented.[1,2]

Japanese clinical practice guidelines for dystonia and multiple review articles indicated a change to clozapine, but only small-scale open-label studies and case reports have confirmed its efficacy.[3-6] In cases of treatment-resistant schizophrenia, it is desirable to introduce clozapine after considering the side effects that are likely to occur with

its administration. Botulinum toxin is effective only for focal dystonia, but there are currently very few reports on antipsychotic-induced dystonia.[3,6–8] Additionally, off-label use of tetrabenazine,[3,6–8] benzodiazepine receptor agonists,[3,7,8] baclofen,[3,7,8] and amantadine[5,7] has been proposed in Japan, but there is insufficient evidence, and such use is not recommended.

There were no findings regarding the preventive effects of specific treatments on tardive dystonia, including the selection of antipsychotics, concomitant use of anticholinergics, and concomitant use of antihistamines. A retrospective investigation of the frequency of tardive dystonia in 80 patients who were non-senile, had schizophrenia, had never received first-generation antipsychotics (FGAs), and had been taking second-generation antipsychotics (SGAs) for at least 1 year showed that 11 of 78 cases (14.1%) were affected by tardive dystonia.[9] In addition, a report on Japanese subjects regarding the frequency of tardive dystonia due to FGA administration[10] showed that tardive dystonia occurred in 15 of 716 patients (2.1%), and a study of Dutch patients[11] showed that tardive dystonia occurred in 26 of 194 (13.4%) hospitalized patients (64.7% of whom received long-acting injections of FGAs). Direct comparisons are not possible due to differences in study design, but based on these findings, there is currently no clear answer regarding the preventive effect of SGAs on tardive dystonia, and there is no consensus for a specific drug.

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CHAPTER 4: OTHER SIDE EFFECTS OF ANTIPSYCHOTICS

CQ4-1: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR MALIGNANT NEUROLEPTIC SYNDROME?

Semi-recommendation

If malignant neuroleptic syndrome is suspected, then it is desirable to discontinue antipsychotic administration and conduct intensive physical therapy and management (including fluid replacement; ventilation as needed; and monitoring of temperature, pulse, and blood pressure), as well as carefully exclude other physical diseases and confirm a definitive diagnosis.

Dantrolene therapy for malignant neuroleptic syndrome carries the risk of liver dysfunction but is suitable because it reduces mortality and improves malignant neuroleptic syndrome.

Bromocriptine therapy for malignant neuroleptic syndrome has a risk of worsening psychiatric symptoms but is suitable because it reduces mortality and improves malignant neuroleptic syndrome.

Electroconvulsive therapy (ECT) for malignant neuroleptic syndrome has not been shown to reduce mortality but is used because it may improve psychiatric symptoms and malignant neuroleptic syndrome.

To prevent malignant neuroleptic syndrome, it is desirable to avoid polypharmacy, rapid dose increases or decreases, use of high-potency first-generation antipsychotics (FGAs), sudden discontinuation of anticholinergics, and high-dose administration of antipsychotics.

Commentary

Malignant neuroleptic syndrome is a life-threatening (potentially fatal, especially in those who are old) serious side effect that presents with various autonomic disorders, including fever, diarrhea, muscle stiffness, confusion, disturbance of consciousness, blood pressure fluctuations, and tachycardia, as well as symptoms such as elevated creatine kinase, rhabdomyolysis, acute renal failure, leukocytosis, and abnormal liver function.[1-8] The incidence of malignant neuroleptic syndrome is 0.01%–3%,[1,9–11] and its risk factors include psychotic symptoms, organic brain disorders (neurological disorders), alcohol use disorders, Parkinson's disease, hyperthyroidism, psychomotor agitation, mental retardation, male sex, young age, agitation, dehydration, physical restraints, and bolus or parenteral administration of antipsychotics.[7,8,12–21] Data from Japanese clinical trials and post-marketing surveillance studies generally indicated an incidence of less than 0.5%.[22] Malignant neuroleptic syndrome is a rare, heterogeneous disease and a life-threatening event. Therefore, we searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found.[23] Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies.

No studies comparing the discontinuation and continuation of antipsychotics were found, but antipsychotics were first

discontinued in many studies and in routine clinical practice by specialists, and a failure to do so, can lead to death. Therefore, if malignant neuroleptic syndrome is suspected, it is recommended to discontinue antipsychotic administration and conduct intensive physical therapy and management (including fluid replacement; ventilation as needed; and monitoring of temperature, pulse, and blood pressure), as well as carefully exclude other physical diseases and confirm a definitive diagnosis.[1-5,7] Additionally, attention must be given to the worsening of psychiatric symptoms since antipsychotic therapy is discontinued, and in cases of concomitant use of antipsychotics and anticholinergics, anticholinergic dose reduction or discontinuation may exacerbate the malignant neuroleptic syndrome.[21,24]

Regarding dantrolene therapy for malignant neuroleptic syndrome, in an analysis of a case series that compared a group receiving this therapy with a group that received only physical therapy (n [number of patients] = 734),[25] the mortality rate for the dantrolene use group (9–10%) was significantly lower than that for the physical therapy only group (21%). Additionally, an open-label study in Japan[26] ($n = 27$) showed that dantrolene use improved malignant neuroleptic syndrome in 77.8% of patients. There were no reports of changes in psychiatric symptoms. Liver dysfunction has been reported as a harmful side effect of dantrolene.[27] Concomitant use with calcium channel blockers should be avoided since the possibility of cardiovascular collapse has been indicated.[23] Based on the above reports, dantrolene therapy for malignant neuroleptic syndrome carries the risk of liver dysfunction but is desirable because it reduces mortality and improves malignant neuroleptic syndrome.[1-3,7]

Regarding bromocriptine therapy for malignant neuroleptic syndrome, in an analysis of a case series that compared a group receiving this therapy with a group that underwent only physical therapy ($n = 734$),[25] the mortality rate for the bromocriptine use group (monotherapy group/concomitant therapy group) had a mortality rate (8%–10%) that was significantly lower than that of the physical therapy only group (21%). Additionally, of 95 cases of malignant neuroleptic syndrome that underwent concomitant bromocriptine therapy, 88% (83 cases) exhibited reduced symptoms of malignant neuroleptic syndrome, and of the 54 cases that underwent bromocriptine monotherapy, 94% (51 cases) showed clinical improvement.[25] However, worsening of psychiatric symptoms has been reported as a harmful side effect of bromocriptine.[28,29] Based on the above reports, bromocriptine therapy for malignant neuroleptic syndrome has a risk of worsening psychiatric symptoms but is desirable because it reduces mortality and improves malignant neuroleptic syndrome.

Regarding ECT for malignant neuroleptic syndrome, a case series ($n = 734$)[30] showed that the mortality rates of the ECT group ($n = 29$) and the group that did not receive specific therapy were 10.3% and 21%, respectively. Although a decreasing tendency was observed, the difference was not statistically significant. In another case series ($n = 45$), ECT improved malignant neuroleptic syndrome and psychiatric symptoms in approximately 90% of cases, but cardiovascular side effects and hyperkalemia were also observed.[31] Based on the above reports, ECT for malignant neuroleptic syndrome has not been shown to reduce mortality but is desirable because it may improve psychiatric symptoms and the malignant neuroleptic syndrome.

Regarding other therapies, there have been reports on amantadine,[25] benzodiazepine receptor agonists,[32,33] L-DOPA,[34] apomorphine,[35] and carbamazepine,[36] but the sample sizes for each study were small, and there is insufficient evidence to reach a conclusion.[7]

Regarding findings related to the prevention of malignant neuroleptic syndrome, a case–control study[16] of patients with malignant neuroleptic syndrome ($n = 67$) and control patients ($n = 254$) showed that the type of and change in antipsychotic dose, rather than the total antipsychotic dose, were directly related to the malignant neuroleptic syndrome. Moreover, to prevent malignant neuroleptic syndrome, it is desirable to avoid polypharmacy, rapid dose increases or decreases, use of high-potency FGAs, sudden discontinuation of anticholinergics, and high-dose administration of antipsychotics.[3,7,16] Additionally, a case series study ($n = 44$), in which antipsychotics were resumed after improvement of malignant neuroleptic syndrome, recommended a withdrawal period of at least five days.[3,7,37] Starting with very low doses and closely monitoring physical and biochemical parameters is the preferred course of action.[3,7] Additionally, when resuming antipsychotics, it is desirable to consider the use of drugs that are structurally different from the antipsychotics that caused the malignant neuroleptic syndrome or those with low affinity for dopamine receptors (e.g., quetiapine and clozapine) and to avoid the use of long-acting injections and high-potency FGAs.[3,7,16,37–39]

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CQ4-2: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR WEIGHT GAIN DUE TO ANTIPSYCHOTICS?

Semi-recommendation

It is desirable to implement lifestyle interventions, including weight measurements, dietary changes, nutritional education, and exercise, as therapies for weight gain caused by antipsychotics. Antipsychotic dose reduction does not lead to weight loss and should not be implemented. Changing to an antipsychotic with a low risk of weight gain should be considered after weighing the benefits and harms, while carefully monitoring the exacerbation of psychiatric symptoms.

As a preventive measure against weight gain due to antipsychotics, it is desirable to measure body weight regularly before and after starting any antipsychotic.

Commentary

Weight gain is a side effect that is often experienced with antipsychotics, especially second-generation antipsychotics (SGAs),[1–4] and may be a risk factor for metabolic disorders and cardiovascular diseases, leading to worsened outcomes. The number of individuals who are obese is increasing worldwide, particularly among those who are young and in developed countries.[5] Against the backdrop of such an increase in the number of people who are obese, the effects of antipsychotics on weight gain have become a risk factor for various metabolic diseases. Additionally, adherence to antipsychotics may decrease due to an obesity-related negative body image, which may result in the worsening of psychiatric symptoms. Therefore, weight gain is an adverse effect that should be avoided or ameliorated not only from the perspective of improving psychiatric symptoms but also from the perspective of vital prognosis and quality of life (QOL).[6] In terms of pathophysiology, weight gain is associated with the histamine H_1 receptor and serotonin

5-HT_{2C} receptor affinities of antipsychotics.[7,8] It has also been reported that the lifestyle characteristics of patients with schizophrenia, such as the lack of dietary restrictions or lack of exercise, may also affect weight gain.[9] We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies.

A meta-analysis of 17 RCTs that investigated the effects of lifestyle interventions (behavioral intervention, self-monitoring, dietary modification, nutrition education, and exercise) on weight gain in patients who were obese (body mass index (BMI) ≥ 25 kg/m^2, BMI ≥23 kg/m^2 for Asians) and aged 18 years or older with severe mental disorders confirmed that lifestyle interventions had a slight but significant effect on weight loss at 6 and 12 months after the usual treatment.[10] However, among the outcomes listed in this meta-analysis, only the improvement in weight gain was addressed; factors such as inconsistency and indirectness that affected the quality of evidence were significant, so a recommendation was not made. The "Maudsley Prescribing Guidelines in Psychiatry 13th Edition" also recommends a behavioral lifestyle program that is aimed mainly at improving diet and increasing physical activity,[11] and it states that antipsychotics should be used with lifestyle interventions to prevent weight gain.

In CQ2-2, no significant differences in weight loss were found between patients with stable schizophrenia receiving antipsychotic dose reduction and those receiving antipsychotic dose maintenance. Therefore, dose reduction was not recommended, and this conclusion was also adopted in the present CQ. There is a systematic review of RCTs that compared the effectiveness of changing antipsychotics and continuing the same drug as interventions for weight gain and adverse metabolic events associated with antipsychotics in patients with schizophrenia or schizophrenic spectrum disorders.[12] No effect was observed with drug change, but the results were difficult to interpret because of bias from the high study withdrawal rate in the drug change group. However, guidelines in other countries recommend switching to antipsychotic drugs that have a low risk of weight gain when weight gain is observed.[11,13,14] As with other drug-induced side effects, it is generally self-evident when antipsychotic side effects appear to reduce the dose of the causative drug, temporarily discontinue the drug in severe cases, carefully consider the advantages and disadvantages of dose reduction or discontinuation when administering other antipsychotics, and carefully consider if the causative drug is effective for psychiatric symptoms. Therefore, such actions should be considered after weighing the benefits and harms while monitoring the worsening of psychiatric symptoms.

A systematic review that included a meta-analysis of placebo-controlled, double-blind RCTs was reported, where antipsychotic-induced metabolic adverse events in schizophrenia were set as the primary endpoint.[15] Metformin and aripiprazole were more effective than placebo, but metformin is only covered by Japanese national health insurance for type 2 diabetes, and aripiprazole is not recommended for concomitant use with other antipsychotic drugs. CQ1-3 suggests not using concomitant antipsychotic therapy, and moreover, long-term adverse events are unknown. Therefore, neither metformin nor aripiprazole was recommended. Similarly, an RCT indicated that liraglutide improved weight gain induced by olanzapine and clozapine [n (number of patients) = 103][16]; however, in Japan, liraglutide is covered by national health insurance only for type 2 diabetes, so it was not listed as a semi-recommendation.

To prevent weight gain due to antipsychotics, it is desirable to measure body weight regularly before and after administration of any antipsychotic, and international guidelines state that regular weight measurements are effective for preventing weight gain.[11,17,18] It is recommended that the measurement interval be shorter in children and adolescents than in adults and that the height be measured at the same time.[18] Pillinger et al. conducted a network meta-analysis of RCTs on weight, BMI, etc. with 18 antipsychotic drugs (*N* [number of studies] = 100, *n* = 25 952), and the results showed that weight gain and other metabolic side effects should be monitored when administering clozapine and olanzapine.[19] Guidelines from other countries also indicate that clozapine and olanzapine are associated with a high risk of weight gain.[11,13] According to frequency information in Japanese clinical studies,[20] the first-generation antipsychotic (FGA) haloperidol was reported to cause weight loss (7%); no weight gain was reported. With SGAs, weight gain occurred at high frequencies, at approximately 15% for clozapine, olanzapine, and paliperidone, and approximately 2%–7% for other SGAs.

Based on the above reports, when the prevention of weight gain during pharmacological therapy with antipsychotics is necessary, it is desirable to educate patients and their families about the risks of weight gain and other metabolic side effects for each drug; Furthermore, SDM about the administered drugs will lead to improved adherence.

Finally, please refer to the "Prevention Guide for Obesity and Diabetes in Patients with Schizophrenia" for details not only on weight gain but also on diabetes prevention and therapies.[21]

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CQ4-3: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR CONSTIPATION DUE TO ANTIPSYCHOTICS?

Semi-recommendation

If chronic constipation occurs while taking antipsychotics, then firstly, identifying its cause is necessary by considering the effects of physical diseases such as colon cancer and Crohn's disease, other psychotropics, and concomitant use of other drugs. Drugs with anticholinergic effects (e.g., antidepressants, antipsychotics, antiparkinsonian drugs, benzodiazepine receptor agonists, and first-generation antihistamines) are listed as drugs that tend to cause chronic constipation, so avoiding their concomitant use with antipsychotics is preferred.

In the case of constipation caused by antipsychotics, they should be continued if the causative drugs are effective for psychiatric symptoms, symptoms are not aggravated (e.g., leading to an ileus), and there are no problems with the patient's drug tolerance. Additional administration of lactulose, polyethylene glycol preparations, and sodium picosulfate may improve constipation, but new side effects should be noted. Appropriate exercise, use of nutritional supplements, and sufficient fluid intake are desirable for improving constipation.

To prevent constipation, it is desirable to detect constipation susceptibility at an early stage by physical examinations, such as auscultation, palpation, and percussion, as well as by medical interviews. Avoiding concomitant use of the above drugs, which tend to cause chronic constipation, with antipsychotics is preferred. When selecting antipsychotics, drugs that are unlikely to cause constipation should be considered.

Commentary

Although the prevalence of chronic constipation in the general population varies between reports (2%–27%), the 2013 National Lifestyle Survey by the Ministry of Health, Labour and Welfare reported that 2.6% of males and 4.9% of females complained of constipation, whereas in the United States, the value was 15% across all ages.[1-3] There are currently no large-scale studies that examined the prevalence of constipation in patients with schizophrenia or in patients taking psychotropics, including antipsychotics. We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies.

For chronic constipation that occurs while taking antipsychotics, it is necessary to consider other physical diseases such as colorectal cancer and Crohn's disease, other psychotropics, and other causes such as the concomitant use of other drugs and to conduct a differential diagnosis. Treatment should be conducted according to the cause. Japan's "Chronic Constipation Clinical Practice Guideline 2017" states that "chronic constipation is more likely to occur due to pharmacological effects, such as the inhibitory effects of drugs with anticholinergic effects (e.g., antidepressants, some antipsychotics, antiparkinsonian drugs, benzodiazepine receptor agonists, and first-generation antihistamines) on gastrointestinal motility, peristalsis, intestinal juice secretion, and anticholinergic effects of psychotropics (antipsychotics and antidepressants)".[1] Therefore, the prevalence of constipation is higher in patients with schizophrenia taking these drugs for long periods of time than in the general population. Such cases are more likely to become serious, so it is desirable to avoid the concomitant use with antipsychotics. Psychotropics, such as antipsychotics and antiparkinsonian drugs used to prevent side effects, reduce intestinal motility, causing stagnation of fecal mass, which continues to physically stretch as the intestinal wall expands. As a result, the intestinal smooth muscle ruptures, the muscle layer thins, degeneration

of Auerbach's plexus within the muscle layer occurs, and peristaltic function declines, resulting in a vicious cycle. Thus, an ileus may easily occur from increasing the dose of antipsychotics or adding antiparkinsonian drugs. Sepsis may also occur due to decreased intestinal barrier function and immune function.[4]

As with other drug-induced side effects, it is generally self-evident when antipsychotic side effects occur to reduce the dose of the causative drug, temporarily discontinue it in severe cases, carefully consider the advantages and disadvantages of dose reduction or discontinuation when administering other antipsychotics, and carefully consider if the causative drug is effective for psychiatric symptoms. Only a few high-quality studies have been conducted on this action. However, it was mentioned in the World Federation of Societies of Biological Psychiatry guidelines that, if the causative drug is effective toward psychiatric symptoms and does not cause serious symptoms such as an ileus or if there are no problems with patient tolerance, then antipsychotics should be continued.[5] For the therapeutic interventions in these cases, a retrospective study by De Hert et al., in which the frequency of laxative use was electronically recorded,[6] recommended additional laxatives such as lactulose, polyethylene glycol, and sodium picosulfate, as well as non-pharmacological interventions to promote appropriate exercise, use of nutritional supplements, and adequate fluid intake.[5]

There is also insufficient evidence for the prevention of antipsychotics-induced constipation. In the only instance, in the World Federation of Societies of Biological Psychiatry guidelines, a recommendation was made for the use of antipsychotics that minimize the risk of constipation and for its early detection through physical examinations such as auscultation, palpation, and percussion.[5] Meanwhile, sufficient evidence has not been obtained from comparative studies on the risks of individual drugs, so this guideline presents frequency information from Japanese clinical research.[7] The incidence of constipation was approximately 30% with clozapine; approximately 5%–15% with haloperidol, olanzapine, risperidone, blonanserin, paliperidone, perphenazine, quetiapine, and aripiprazole; and approximately 3% with asenapine, brexpiprazole, and lurasidone.

Although frequent and potentially severe, compared with that for other side effects and general constipation, there is a lack of evidence both in Japan and overseas on constipation due to antipsychotics, so further understanding is strongly needed.

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CQ4-4: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR QT PROLONGATION DUE TO ANTIPSYCHOTICS?

Semi-recommendation

Considering that all antipsychotics have the risk of inducing QT prolongation, it is desirable to implement periodic monitoring. For QT prolongation that occurs while taking antipsychotics, there is a need to examine physical conditions such as arrhythmias and electrolyte abnormalities, the concomitant use of drugs with a risk of QT prolongation (including psychotropics), and the number and dosage of antipsychotics, as well as the need to identify the antipsychotic-induced QT prolongation. When the QTc is 500 ms or more, a cardiologist should be consulted immediately to determine the treatment strategy. If the QT prolongation is caused by an antipsychotic, then it is desirable to reduce the antipsychotic dose or switch to a pharmacological therapy that is less likely to cause QT prolongation.

As preventive measures for QT prolongation, intravenous administration of antipsychotics, administration that exceeds the maximum dose, and polypharmacy should be avoided to the extent possible.

Commentary

QT prolongation syndrome is characterized by QT prolongation accompanied by abnormal T wave morphology on electrocardiogram, and an unusual ventricular tachycardia called torsade de pointes or severe ventricular arrhythmia such as ventricular fibrillation may occur, leading to cerebral ischemic symptoms, dizziness, syncope, and sudden death.[1] Concomitant underlying heart diseases such as heart failure, cardiomyopathy, coronary artery disease, hypertension, and left ventricular hypertrophy accelerate this QT prolongation.[1] QT prolongation is common among women and individuals who are middle-aged or older, and it is often caused by electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia).[1] QT prolongation is also associated with metabolic disorders such as diabetes, anorexia nervosa, pituitary insufficiency, and hypothyroidism.[1] The QT interval on an electrocardiogram constantly fluctuates due to various factors, particularly heart rate, so evaluation using a heart rate-corrected value (QTc) is common. Additionally, QT prolongation syndrome has no subjective symptoms, necessitating monitoring by periodic electrocardiography at least once a year.

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching,

such as that obtained from observational studies. As with other drug-induced side effects, it is generally self-evident when antipsychotic side effects occur to reduce the dose of the causative drug, temporarily discontinue it in severe cases, carefully consider the advantages and disadvantages of dose reduction or discontinuation when administering other antipsychotics, and carefully consider if the causative drug is effective for psychiatric symptoms. A few high-quality studies have been conducted but with no conclusive results. Nevertheless, the lack of substantial results does not constitute a basis for disregarding the self-evident nature of this action. The general principles for QT prolongation due to antipsychotics are described below first, after which we describe therapies to consider when it is difficult to address these general principles.

First, for QT prolongation therapy, there is a need to examine physical conditions such as arrhythmias and electrolyte abnormalities as mentioned above, concomitant use of drugs with a risk of QT prolongation (including psychotropics), and the number and dosage of antipsychotics, as well as the need to identify the antipsychotic-induced QT prolongation. If the QT prolongation is caused by antipsychotics, the antipsychotic dose should be reduced, or the pharmacological therapy should be changed to one that is less likely to cause QT prolongation.[2,3] QT prolongation is frequently observed during multi-drug therapy with antipsychotics and monotherapy should be attempted in these situations. Meanwhile, if the QTc is 500 ms or more, then a cardiologist should be consulted immediately.[1]

According to the results of guidelines in other countries and network meta-analyses, antipsychotic therapies reported to likely cause QT prolongation include intravenous antipsychotics, administration exceeding the maximum dose, and polypharmacy.[4-6] Sufficient evidence has not been obtained from comparative studies on the risks of individual drugs, so this guideline presents frequency information from Japanese clinical research.[7] Quantitative ranking is difficult, and this should be understood as a framework for clinical reference. All antipsychotics have the risk of inducing QT prolongation, but all have been reported as less than 2%.

Regarding preventive methods for QT prolongation, all antipsychotics can cause this disorder. Thus, when using antipsychotics, it is desirable to carefully consider the patient's initial history and to avoid intravenous antipsychotics, administration exceeding the maximum dose, and polypharmacy to the extent possible.[2,8,9]

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CQ4-5: WHAT ARE RECOMMENDED TREATMENT AND PREVENTION FOR SEXUAL DYSFUNCTION DUE TO ANTIPSYCHOTICS?

Semi-recommendation

Patients rarely complain about sexual dysfunction that occurs while taking antipsychotics, so a physician should interview the patient for evaluation. For sexual dysfunction that occurs while taking antipsychotics, it is necessary to exclude the effects of physical diseases, other drugs, and the schizophrenia itself and identify that the sexual dysfunction is caused by the antipsychotics. When sexual dysfunction due to antipsychotics occurs, then as a rule, the causative drug dose should be reduced, and in severe cases, the drug should be temporarily discontinued and another antipsychotic administered. If the causative drug is effective for psychiatric symptoms, then the advantages and disadvantages of its dose reduction or discontinuation should be carefully considered.

There is insufficient evidence supporting preventive methods for sexual dysfunction caused by antipsychotics.

Commentary.

Sexual dysfunction includes defined symptoms such as decreased libido, erectile or orgasm dysfunction, menstrual disorders or amenorrhea, galactorrhea, and breast enlargement, as well as hyperprolactinemia, and even more broadly, changes in test results such as increased blood prolactin. Sexual dysfunction is more common in men than in women (49%–59% vs. 25%–49%, respectively). Decreased libido, erectile dysfunction, and ejaculation disorders are more common in men, while amenorrhea and decreased libido are more common in women.[1-3] As described above, despite the high frequency of sexual dysfunction, patients rarely complain about sexual

dysfunction that occurs while taking antipsychotics. Thus, a physician should evaluate the patient through interview. Additionally, although sexual dysfunction frequently occurs while taking antipsychotics, there is a need to exclude the effects of physical diseases, other drugs, and schizophrenia itself, and to verify that the sexual dysfunction is caused by the antipsychotics. The frequency of sexual dysfunction is relatively high at approximately 38% in both healthy men and women.[2] Thus, there is a need to understand that this is not a problem unique to patients with schizophrenia taking antipsychotics.

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies. As with other drug-induced side effects, it is generally self-evident when antipsychotic side effects occur to reduce the dose of the causative drug, temporarily discontinue it in severe cases, carefully consider the advantages and disadvantages of dose reduction or discontinuation when administering other antipsychotics, and carefully consider if the causative drug is effective for psychiatric symptoms. A few high-quality studies have been conducted but with limited results. Nevertheless, the lack of substantial results does not constitute a basis for disregarding the self-evident nature of this action.

Studies on switching from first-generation antipsychotics (FGAs) to second-generation antipsychotics (SGAs) have shown inconsistent results for conditions such as sexual dysfunction, worsening psychiatric symptoms, and extrapyramidal symptoms,[4,5] and studies on switching between SGAs also found no significant differences in sexual dysfunction and psychiatric symptoms.[6,7] Therefore, no consistent results were obtained regarding changes in antipsychotic medications. Insufficient evidence was found regarding improvements in sexual dysfunction and hyperprolactinemia caused by antipsychotic dose reductions. There are no clear recommendations for dose reductions in the guidelines from multiple countries. When considering improvements from dose reductions, it is desirable to consider the patient's condition, the balance between the benefits of improving hyperprolactinemia and sexual dysfunction, and the harm of worsening psychiatric symptoms.

Reports on concomitant therapy include RCTs analyzing the concomitant use of small doses of aripiprazole,[8-12] an RCT on the concomitant use of Shakuyaku-kanzo-to,[13] and an RCT on the concomitant use of sildenafil[14]; however, these are small studies, and concomitant use is not recommended due to the lack of reliable and consistent results for improvements in sexual dysfunction and psychiatric symptoms. The concomitant use of small doses of aripiprazole has been reported to reduce prolactin levels, but CQ1-3, which has a higher level of evidence and is positioned as a recommendation, does not recommend the concomitant use of antipsychotics; thus, concomitant use of aripiprazole is not recommended here. The main side effect of Shakuyaku-kanzo-to is hypokalemia in 0.2% of cases,[15] and glycyrrhiza is likely to cause pseudoaldosteronism.[16]

There are no systematic reviews or RCTs on preventive methods, and sufficient evidence does not exist. There are no clear recommendations for prevention even in international guidelines, and in the World Federation of Societies of Biological Psychiatry and European College of Neuropsychopharmacology guidelines, the only comment on the prevention of hyperprolactinemia due to antipsychotics is to select antipsychotics with minimal or no increase in prolactin levels.[17,18] Meanwhile, sufficient evidence has not been obtained from comparative studies on the risks of individual drugs, so this guideline presents frequency information from Japanese clinical research.[19] Quantitative ranking is difficult, and this should be understood as a framework for clinical reference. Most antipsychotics are known to increase blood prolactin levels through dopamine receptor antagonism. Therefore, in general, the frequency of "elevated blood prolactin" is high (≤80%), but the "hyperprolactinemia" and "menstrual disorders" that are thought to result from this are less frequent (≤7%), with "galactorrhea" and "amenorrhea" occurring less frequently (≤3%). Elevated blood prolactin occurs at high frequencies of 25%–80% with risperidone and its long-acting injections as well as with paliperidone and its long-acting drugs, followed by frequencies of approximately 15% with blonanserin, haloperidol, and clozapine and frequencies of less than a few percent with other drugs. Decreased blood prolactin has been reported for aripiprazole (approximately 40%) and quetiapine (approximately 5%). There is a large discrepancy between the frequency of increased blood prolactin and the frequency of sexual dysfunction, so this should be used as a reference with the understanding that the selection of drugs that do or do not increase blood prolactin levels does not necessarily lead to the prevention of sexual dysfunction.

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CHAPTER 5: TREATMENT-RESISTANT SCHIZOPHRENIA

CQ5-1: IS CLOZAPINE USEFUL IN TREATMENT-RESISTANT SCHIZOPHRENIA?

Recommendation

For treatment-resistant schizophrenia, compared with other antipsychotics, clozapine improves psychiatric symptoms (B), shows similar treatment continuation rate (D) and quality of life (QOL) (D), has a higher incidence of adverse events (C), and has a lower incidence of extrapyramidal symptoms (C).

Based on this evidence, clozapine is an effective drug for treatment-resistant schizophrenia. Although attention should be paid to the occurrence of side effects, its use is recommended (1C).

Commentary

Clozapine is listed as a first-line treatment for treatment-resistant schizophrenia in the current international guidelines in each country and is the only drug approved for treatment in Japan with a specific indication for treatment-resistant schizophrenia. In Japan, clozapine is indicated for treatment-resistant schizophrenia, which includes cases of inadequate response and intolerance.[1] The inadequate response is defined as a failure to respond (never reached ≥41 points in the Global Assessment of Functioning) to a sufficient dose (≥600 mg/d chlorpromazine equivalent) of at least two well-tolerated antipsychotics with sufficient treatment duration (at least 4 weeks). Intolerance refers to cases in which the dose cannot be increased sufficiently due to extrapyramidal symptoms. In this CQ, treatment-resistant schizophrenia is defined relative to inadequate response to clozapine administration so that the recommendations will be useful for clinical practice in Japan.

In regard to the improvement in psychiatric symptoms, Siskind et al. conducted a meta-analysis that compared the efficacy and tolerability of clozapine and other antipsychotics in patients with treatment-resistant schizophrenia (*N* [number of studies] = 25; *n* [number of patients] = 2364).[2] This report indicated that, compared with other antipsychotics, clozapine significantly improved short-term general psychotic symptoms, positive symptoms, and negative symptoms (less than 3 months) (general psychotic symptoms: standardized mean difference = −0.39, 95% CI: −0.61 – −0.17, $p = 0.0005$; positive symptoms: standardized mean difference = −0.27, 95% CI: −0.47 – 0.08, $p = 0.006$; negative symptoms: standardized mean difference = −0.25, 95% CI: −0.40 – −0.10, $p = 0.00091$). Clozapine did not show significant improvements in long-term general psychotic symptoms and negative symptoms but did significantly improve long-term positive symptoms (standardized mean difference = −0.25, 95% CI: −0.43 – −0.07, $p = 0.006$). Therefore, compared with other psychotics, clozapine improves psychiatric symptoms in treatment-resistant schizophrenia (B).

Regarding all-cause treatment discontinuation, a pairwise comparison by Samara et al. showed no significant differences in direct comparisons with olanzapine, risperidone, chlorpromazine, haloperidol, and ziprasidone.[3] Additionally, a network meta-analysis in the same report showed no significant differences in treatment continuation rates between clozapine and other antipsychotics. Therefore, there is no difference in the treatment continuation rate between clozapine and other drugs (D).

Regarding the improvement in the QOL, there are two studies that investigated the effects of second-generation antipsychotics (SGAs) and clozapine on the QOL in treatment-resistant schizophrenia. Naber et al. conducted a 26-week, double-blind, randomized controlled trial (RCT) ($n = 114$) in which clozapine or olanzapine treatment was assigned to patients with schizophrenia who were refractory or intolerant to one or more antipsychotics other than clozapine. The results did not show any significant differences between the two groups.[4] Additionally, Lewis et al. conducted a 52-week, rater-blind RCT ($n = 136$) in patients with treatment-resistant schizophrenia in which clozapine and other SGAs

were assigned to investigate their effects on QOL; however, they found no significant differences between clozapine and other SGAs.[5] These results did not provide clear evidence that clozapine improved the QOL of patients with treatment-resistant schizophrenia (D).

Regarding the increase in adverse events except extrapyramidal symptoms, the above-mentioned meta-analysis by Siskind et al. showed that, compared with other antipsychotics, clozapine had a significantly higher incidence of the common side effects salivation (number needed to harm (NNH) = 4), tachycardia (NNH = 7), sedation (NNH = 7), dizziness (NNH = 11), constipation (NNH = 12), convulsion (NNH = 17), fever (NNH = 19), and nausea / vomiting (NNH = 19); significantly lower incidence of thirst (NNT = 7) and insomnia (NNT = 13); and no differences in hypertension, headache, and weight gain.[2] Therefore, all adverse events, except extrapyramidal symptoms, are common with clozapine (C). Additionally, the appearance of infrequent but serious side effects such as agranulocytosis, neutropenia, myocarditis, cardiomyopathy, and thromboembolism[6] should be carefully monitored; these are described in detail in CQ5-2.

Regarding the improvement in extrapyramidal symptoms, in the previously mentioned meta-analysis by Samara et al., a pairwise comparison showed that clozapine was significantly less likely to be used with an antiparkinsonian drug than risperidone (odds ratio 0.09, 95% CI: 0.01–0.40).[3] Additionally, a network meta-analysis conducted within the same study showed that clozapine was associated with significantly less treatment with antiparkinsonian drugs than risperidone and haloperidol. Therefore, clozapine causes fewer extrapyramidal symptoms than other antipsychotics (C).

Increased mortality and decreased suicide were important outcomes, but no clear evidence was available for either.

Based on this evidence, clozapine is an effective drug for treatment-resistant schizophrenia, and although attention should be given to the occurrence of side effects, the use of clozapine is strongly recommended (1C).

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CQ5-2: WHAT IS RECOMMENDED WHEN SIDE EFFECTS OCCUR IN CASES WHERE CLOZAPINE IS EFFICACIOUS?

Semi-recommendation

In this CQ, we address neutropenia/agranulocytosis, myocarditis/cardiomyopathy, convulsion, salivation, and fever, which are characteristic side effects of clozapine. When clozapine-related side effects occur, then as with other drugs, the clozapine dose should first be reduced, and in cases of severe side effects, temporary discontinuation should be considered. However, in situations where clozapine is effective, continued administration may be necessary even when side effects occur. When attempting additional pharmacological treatment for side effects, the possibility that other side effects may develop must always be considered.

Commentary

In this CQ, we address neutropenia/agranulocytosis, myocarditis/cardiomyopathy, convulsion, salivation, and fever, which are characteristic side effects of clozapine. Please refer to Chapters 3 and 4 of this guideline for countermeasures against side effects that are commonly observed with antipsychotics in general, and not just clozapine, (e.g., weight gain, extrapyramidal symptoms, constipation, QT prolongation, and sexual dysfunction). We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but sufficient evidence related to the topics in this CQ was not found. We therefore created a semi-recommendation and commentary that included evidence retrieved by hand search, such as that from observational studies.

1. Neutropenia/agranulocytosis

According to an epidemiological observational study, approximately half the patients who developed neutropenia/agranulocytosis with clozapine developed symptoms within 18 weeks after the start of administration[1] and reported that symptom expression peaked in the first 12 weeks.[2] The occurrence of neutropenia and agranulocytosis is not reported to be clozapine dose-dependent.[1,2] In Japan, the clozapine administration method and dose are described in the package insert (starting at 12.5 mg/day and gradually increasing to the therapeutic dose), and the frequency and blood monitoring procedures are specified in the Clozaril® Patient Monitoring Service (CPMS) operational procedure. Concomitant use of valproate has been reported to increase the risk of developing neutropenia,[3] so caution should be exercised regarding concomitant drugs.

The basics of managing neutropenia and agranulocytosis are described in the CPMS operational procedure.[4] If the blood test results are "white blood cell count < 3,000/mm^3 or neutrophil count < 1,500/mm^3," then clozapine should be discontinued and administration and a hematologist consulted. In cases with a "neutrophil count ≥ 500/mm^3 and <1,000/mm^3 and body temperature ≥38°C," a hematologist should be consulted immediately (as a rule, administration of antibacterial agents is needed). In cases where the "neutrophil count <500/

mm^3," a hematologist should be consulted immediately and protective isolation should be considered. In cases where the "neutrophil count $<500/mm^3$ and body temperature ≥38°C," generally, hematologists will initiate agranulocytosis therapy. If there is a medical cooperation agreement, then the patient will be transported to the partner medical institution and treated by a hematologist or, alternatively, treated according to the instructions of the hematologist at the collaborating medical institution (broad-spectrum antibacterial agents are administered and administration of granulocyte colony-stimulating factor (G-CSF) preparations and antifungal drugs is considered). The Ministry of Health, Labour and Welfare's Manual for Management of Individual Serious Adverse Drug Reactions is also useful.[5]

Lithium has been reported to be effective in adults and children with clozapine-related neutropenia,[6-11] and the "Maudsley Prescribing Guidelines in Psychiatry 13th Edition" describes the prescription of lithium 400 mg/day (dose at night) and titrating until the plasma concentration is >0.4 mmol/L as a method of using lithium to restore the white blood cell count to within the reference range.[12] However, it should be noted that the concomitant use of lithium cannot prevent agranulocytosis[13,14] and is the off-label prescribing in schizophrenia.

On June 3, 2021, the package insert and CPMS of clozapine were revised as follows, implementing the same deregulations as applied overseas: (1) from week 52 onwards, blood monitoring can be conditionally performed every 4 weeks; (2) the re-administration review criteria stipulated in the CPMS operational procedure manual will be deregulated, and at the same time, the package insert will allow conditional re-administration to patients who have previously discontinued administration of this drug according to the blood test discontinuation criteria stipulated by CPMS; and (3) the drug can be administered to patients with a history of agranulocytosis or severe neutropenia.

2. Myocarditis/cardiomyopathy

The basics of how to manage myocarditis and cardiomyopathy are described in the guidance for the appropriate use of clozapine.[4] The Guidelines for Diagnosis and Treatment of Myocarditis created by the Japanese Circulation Society Joint Working Group can also serve as a reference.[15]

Before starting clozapine treatment, the presence or absence of cardiac dysfunction should be confirmed by electrocardiography, and the subjective symptoms and physical findings of the patient should be carefully observed after clozapine administration. Myocarditis should be suspected if symptoms of heart failure (such as shortness of breath, dyspnea, fatigue, and edema), chest pain, heart block, or arrhythmia occur for no other reason after starting clozapine treatment. If symptoms of heart failure are observed, then electrocardiography and blood tests should be conducted immediately. Blood biochemical tests will show transient increases in CRP, AST, LDH, CK-MB (creatine kinase-myocardial band), and myocardial constituent proteins such as cardiac troponin T in the blood. In particular, the rapid measurement of cardiac troponin T by the enzyme-labeled antibody method is simple and useful.[15] If any abnormal findings or changes are observed via electrocardiography, then a cardiologist should be consulted immediately and appropriate measures should be taken, such as detailed examination and consideration of drug discontinuation. For early detection of myocarditis, it is desirable to measure troponin and CRP every week for 4 weeks after starting clozapine.[16] Initial signs of cardiomyopathy often include shortness of breath, dyspnea, syncope, dizziness, palpitations, irregular pulse, chest discomfort, chest pain, and fatigue, but it should be noted that asymptomatic cases also exist. If initial signs are observed, then electrocardiography and chest radiography should be conducted, and if any abnormalities are observed, then a cardiologist should be consulted immediately and appropriate measures taken, such as detailed examination and consideration of drug discontinuation, taken.

There is an observational study showing that rapid increases in clozapine dose and concomitant use of valproate increased the incidence of myocarditis.[17] Carefully monitoring the rate of increase in clozapine dose and use of concomitant drugs may be effective from a preventive perspective.

3. Convulsions

If convulsions occur during clozapine administration, then there is a need to first exclude the possibility of convulsions caused by other factors, such as alcohol withdrawal, benzodiazepine receptor agonist withdrawal symptoms, or water intoxication.

The effect of clozapine to lower the threshold for convulsions is dependent on its blood concentration,[18] so dose reduction should be considered if the convulsion is induced by clozapine.[19] When clozapine dose reduction is difficult, then it is desirable to select and use an antiepileptic according to the convulsion type. Valproate is the most used antiepileptic, and in such cases, oral clozapine should be discontinued for 24 h after the convulsion occurred. Clozapine should then be resumed at a reduced dose and valproate administered.[12,20] The concomitant use of valproate may increase the risk of hepatotoxicity,[21] agranulocytosis,[22] and myocarditis.[17] Other antiepileptics, such as lamotrigine, topiramate, and gabapentin, have also been reported to be effective.[18,20] Carbamazepine, phenytoin, and phenobarbital are known to reduce clozapine concentration and should be avoided considering their side effects.[18] Patients with a history of epilepsy should be carefully monitored, and the dose of clozapine should not be increased rapidly.[4] Although epilepsy treatment has changed significantly in recent years with the introduction of new antiepileptics, such treatment should be carefully selected in patients with clozapine-induced convulsions, since there are still few reports on the administration of antiepileptics for clozapine-induced convulsions.

4. Salivation

Clozapine-induced hypersalivation is different from salivation caused by conventional antipsychotics and is more common at rest and at night.[19] Salivation diminishes over time but may persist.[12] Therefore, it is desirable to conduct follow-up observations on the salivation first and then attempt pharmacological treatment if the condition persists.

Among the drugs available in Japan, the antimuscarinic propantheline bromide (N [number of studies] = 6, n [number of patients] = 344) and the antihistamine diphenhydramine ($N = 5$, $n = 334$) are effective.[23] Improvements through the use of the dopamine receptor antagonist metoclopramide[24] as well as biperiden,[25] which has an anticholinergic effect, have been shown in RCTs (one RCT for each drug), but their efficacy has not been established. Thus, when using these drugs, it is necessary to monitor their side effects.

5. Fever

If fever develops, then the possibility of granulocytopenia, malignant syndrome, and clozapine-induced organ inflammation should be carefully considered. For clozapine-induced fever, the body temperature will remain at 38°C or higher for several days, but there will be no physical symptoms other than fever, and symptoms, if present, may be mild.[19] If a high possibility of clozapine-induced fever exists, then one therapy option is the withdrawal of clozapine and resumption after the fever subsides,[19] but there have been several reports of cases where clozapine administration was not stopped.[26-33] The Maudsley Prescribing Guidelines in Psychiatry 13th Edition proposed treating the fever by administering antipyretics after performing a peripheral blood test and gradually increasing the clozapine dose.[12]

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CQ5-3: WHAT IS RECOMMENDED AS A CONCOMITANT THERAPY WHEN CLOZAPINE IS INEFFICACIOUS?

Semi-recommendation

Concomitant therapy with electroconvulsive therapy (ECT) is effective in improving psychiatric symptoms, but it may cause memory impairment and headache. In situations where improvement in psychiatric symptoms is required, the implementation of concomitant ECT, while monitoring adverse events, is desirable.

Concomitant therapy with valproate, lamotrigine, and topiramate may be effective in improving psychiatric symptoms. However, their efficacy is uncertain, and when tolerability is also considered, then the effectiveness of concomitant therapy with any of these drugs is doubtful. None of these drugs are indicated for schizophrenia, and it is believed that they should be carefully introduced only in unavoidable situations where there is a great need to improve psychiatric symptoms, and with the assumption that adverse events will be thoroughly evaluated.

The concomitant therapy with other mood stabilizers, antiepileptics, benzodiazepine receptor agonists, antidepressants, antipsychotics, and other drugs has been shown to be effective, but report only small sample sizes have been published supporting their effectiveness. Moreover, these reports include drugs that have not been approved in Japan. Therefore, concomitant use of clozapine and these drugs is not recommended for the purpose of improving psychiatric symptoms.

Commentary

This CQ addresses concomitant therapy when clozapine is not sufficiently effective for treatment-resistant schizophrenia (so-called "augmentation therapy"). There have been several meta-analyses regarding this CQ in recent years. Although we searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, sufficient evidence was not found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by hand search, such as that obtained from observational studies. Some concomitant therapies have been shown to be effective, but none have been found sufficiently effective to recommend active use.

In regard to concomitant therapy with ECT, a comprehensive meta-analysis of 18 RCTs ($n=1769$)[1] reported that the concomitant ECT group showed efficacy (improvement in psychiatric symptoms) after ECT (standardized mean difference = −0.88, 95% CI: −1.33 – −0.44, $p=0.0001$, $I^2=86\%$) and the subsequent follow-up period (standardized mean difference = −1.44, 95% CI: −2.05 to −0.84, $p<0.00001$, $I^2=95\%$) compared with the clozapine monotherapy group.

Regarding adverse events, compared with the clozapine monotherapy group, the concomitant ECT group showed a significantly higher incidence of memory impairment (risk ratio 16.10, 95% CI: 4.53–57.26, $p<0.0001$, $I^2=0\%$, number needed to harm = 4, 95% CI: 2–14) and headache (risk ratio 4.03, 95% CI: 1.54–10.56, $p=0.005$, $I^2=0\%$, number needed to harm = 8, 95% CI: 4–50), but there was no difference in the therapy discontinuation rate.

Regarding the durability of the effect, an open-label study and case series reported that 32% of cases exhibited relapse after interrupting ECT[2] and that the transient effect of the concomitant therapy with ECT should be considered. Considering the above findings comprehensively, the concomitant use of clozapine and ECT for treatment-resistant schizophrenia has a significant disadvantage in terms of psychiatric symptoms, and in situations where further improvements are required, it is desirable that the risk of adverse events be carefully evaluated before use.

Concomitant therapy of clozapine with valproate, lamotrigine, or topiramate may be effective, but when considering the quality of evidence, strength of effect, adverse events, and concerns about long-term administration, etc., it is difficult to conclude that this approach has a high level of effectiveness.[3] Concomitant therapy with valproate can increase the incidence of myocarditis[4] and granulocytopenia[5] in the early stages of clozapine administration and can also cause the blood concentration of clozapine to fluctuate.[6] Considering the importance of determining the effect of clozapine at the beginning of treatment, concomitant valproate therapy should be avoided in the early stages of clozapine administration. Concomitant therapy with lamotrigine may be effective, but high efficacy cannot be expected with its usage. Concomitant use with topiramate has a significantly higher therapy discontinuation rate than that by the use of valproate alone, suggesting that there is a problem with topiramate tolerability. Therefore, in cases where there is a strong need to improve psychiatric symptoms, careful introduction of the concomitant therapy with these drugs is unavoidable, assuming that adverse events will be thoroughly evaluated.

Regarding the concomitant therapy with other antipsychotics, there are a relatively large number of meta-analyses, but a comprehensive study revealed unclear efficacy.[7] Additionally, given that clozapine is generally prescribed as a single agent, with the exception of cross-titration, which is allowed within 4 weeks of introduction in Japan, concomitant therapy with other antipsychotics is not recommended.

Concomitant use of clozapine with other mood stabilizers, antiepileptics, lithium, antidepressants, benzodiazepine receptor agonists, memantine, *Ginkgo biloba* extract, and glycine lacks sufficient evidence regarding efficacy and adverse events; thus, concomitant therapy with these drugs is not recommended.

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CQ5-4: IF CLOZAPINE IS NOT USED, IS ELECTROCONVULSIVE THERAPY USEFUL FOR TREATMENT-RESISTANT SCHIZOPHRENIA?

Semi-recommendation

The concomitant therapy with antipsychotics other than clozapine and electroconvulsive therapy (ECT) for treatment-resistant schizophrenia may improve psychiatric symptoms in the short term and reduce the occurrence of relapse in the short-to-medium term. On the other hand, possible deterioration of cognitive function has been shown in the short-to-medium term. Therefore, the concomitant therapy of ECT with antipsychotics other than clozapine should be implemented solely in circumstances wherein the use of clozapine presents considerable challenges.

The available evidence is currently insufficient to support the use of ECT without antipsychotics for treatment-resistant schizophrenia, and therefore it is not recommended.

Commentary

The first recipient of ECT by Cerletti and Bini in 1938 was a patient with schizophrenia, who presented symptoms of hallucinations and delusions. For approximately 20 years, until the advent of chlorpromazine, ECT was the main therapy for patients with psychosis. However, owing to the emergence of antipsychotic medications and the prevalent perception of ECT as a stigmatized treatment, ECT is currently established as a therapy for affective disorders, especially severe depression, in many regions, including the United States, Western Europe, and Oceania. Evidence supporting the use of ECT in schizophrenia has emerged, but the clinical studies are small in scale, and many of them have been reported from Asia regions, and there are few high-quality randomized trials. Therefore, major guidelines in each country such as those by the American Psychiatric Association (APA)[1] and the National Institute for Health and Care Excellence (NICE)[2] view the efficacy of ECT for schizophrenia with skepticism and consider it a treatment of last resort for use only when all other alternatives have been exhausted. However, with the advent of the concept of treatment-resistant schizophrenia, there has been increasing awareness about the effectiveness of the concomitant therapy of clozapine and ECT for treatment-resistant schizophrenia (as described in CQ5-3), as well as about the effectiveness of ECT for treatment-resistant schizophrenia[3] and ECT for schizophrenia.[4] In a recently revised guidance on the use of ECT,[5] the perception on the use of ECT changed from "it may be a therapeutic strategy for treatment-resistant schizophrenia" to "it is an effective and safe augmentation strategy." This guideline also emphasizes the necessity to consider whether ECT alone, without the use of clozapine, is effective for treatment-resistant schizophrenia. We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ; however, no adequate evidence was found. Thus, we created a semi-recommendation and commentary that included evidence retrieved by hand search, such as that obtained from observational studies.

Several systematic reviews and meta-analyses of the effects of ECT on schizophrenia have shown that ECT may be more effective than sham ECT in the short term (less than 6 weeks) in improving psychiatric symptoms, preventing relapse, and promoting hospital discharge.[4,6,7] Concomitant therapy of ECT with antipsychotics may yield superior efficacy and expedite symptom improvement compared with antipsychotics alone.[8] However, it should be noted that such evidence does not address the medium- to long-term effects. Known side effects include prolonged convulsions, postictal delirium, headache, myalgia, and nausea, all of which are frequently alleviated with symptomatic therapy.[9,10] The ECT mortality rate is extremely low at approximately 2 out of 100 000 sessions, and ECT is believed to have the same risk rate as general anesthesia or pharmacological therapy.[9–11] Anxiety regarding ECT has been observed at a frequency in 14%–75% of patients, and patients have concerns regarding anesthesia, memory impairment, and brain damage, but there are currently no effective intervention strategies for alleviating these anxieties.[12] Therefore, although concomitant therapy of ECT with antipsychotics for schizophrenia is considered useful in the short term, providing care that addresses the patient's anxiety is also essential.

Indications of ECT for schizophrenia include cases of catatonia, worsening of psychotic state with delusions and hallucinations, suicide attempts, favorable response to previous ECT, and decreased tolerance to antipsychotics.[4] Predictive factors for a favorable response include positive symptoms, young age, short disease duration, absence of family history, high original psychosocial function, good original cognitive function, and paranoid schizophrenia.[4] Predictive factors for a poor response include severe negative symptoms and a long disease duration.[4] Predictive factors for relapse include high doses of antipsychotics before ECT, self-harm, and a high number of ECT sessions.[4] Regarding electrode placement, no difference in effect was observed in the effect between bilateral temporal, bilateral frontal, and unilateral placement, and that bilateral frontal placement was found to be more effective in cases of lower cognitive dysfunction.[4] Regarding

frequency, no difference was observed in cognitive dysfunction between two and three sessions per week, and faster improvements were seen three times per week.[4] Regarding the stimulus dose, no difference was observed in the number of therapies required between the threshold and 1.5 times the threshold; however, the number of sessions required may be higher than that when the target disease is depression.[4,5]

A comprehensive report on ECT for treatment-resistant schizophrenia is a meta-analysis by Sinclair et al.[3] However, many RCTs were included in which ECT was used in combination with clozapine, so only some results could be used to discuss this CQ (i.e., effectiveness of ECT when clozapine is not used). Therefore, in this CQ, among the RCTs in the meta-analysis by Sinclair et al.,[3] we used the results of the RCTs utilizing ECT alone or concomitantly with other antipsychotics other than clozapine that are in Japan.[13-15] Consequently, no study has compared the efficacy of ECT without antipsychotics and with antipsychotic therapy for treatment-resistant schizophrenia. Therefore, owing to insufficient evidence, it is preferable to avoid the use of ECT alone for patients with treatment-resistant schizophrenia.

Next, we will discuss the concomitant therapy with of ECT and antipsychotics. Compared with olanzapine monotherapy, concomitant therapy of ECT and olanzapine produced significant short-term improvements in psychiatric symptoms (N [number of studies] = 1, n [number of patients] = 72, risk ratio 1.91, 95% CI: 1.09–3.36), but exacerbated short-term memory impairment (N = 1, n = 72, risk ratio 27, 95% CI: 1.67–437.68).[14] The concomitant therapy of electroconvulsive therapy and risperidone has been reported to not change the number of categories cleared in the Wisconsin Card Sorting Test over the medium term compared with that of risperidone monotherapy.[15] Regarding relapse, it has been reported that, compared with the antipsychotic monotherapy group, the concomitant ECT and antipsychotic (chlorpromazine) group had a significantly lower rehospitalization rate (N = 1, n = 25, risk ratio 0.29, 95% CI: 0.10–0.85).[13]

Based on the above, compared with clozapine monotherapy or concomitant clozapine and ECT, there is little evidence on the concomitant therapy of ECT and antipsychotics other than clozapine for treatment-resistant schizophrenia, and many of them have been reported from Asia regions and there are no reports on long-term effects. Therefore, the concomitant use of ECT and concomitantly with antipsychotics other than clozapine for patients with treatment-resistant schizophrenia should be implemented only in cases wherein the use of clozapine presents considerable challenges, while considering the common adverse events associated with ECT, including cognitive dysfunction.

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CQ5-5: WHAT IS EFFICACIOUS TREATMENT OTHER THAN CLOZAPINE AND ELECTROCONVULSIVE THERAPY FOR TREATMENT-RESISTANT SCHIZOPHRENIA?

Semi-recommendation

For treatment-resistant schizophrenia, switching to an antipsychotic other than clozapine may improve psychiatric symptoms; however, no drug has been shown to be particularly efficacious.

Based on the above, if a patient with treatment-resistant schizophrenia needs to choose a therapy other than clozapine or electroconvulsive therapy (ECT) for some reason, then switching to a different antipsychotic monotherapy is worth considering. Additionally, in treatment-resistant schizophrenia, concomitant therapy of antipsychotics other than clozapine with other psychotropics is not recommended.

Commentary

Clozapine has the strongest evidence as a pharmacological therapy for treatment-resistant schizophrenia. If clozapine therapy poses challenges towing to environmental factors rather than intolerance or nonresponse, it is desirable to create an environment in which clozapine therapy can be introduced. If this is not possible, then transfer of the patient to a healthcare facility with appropriate infrastructure should be suggested.

There are some cases of treatment-resistant schizophrenia that require consideration of therapies other than clozapine or ECT due to intolerance, nonresponse, or the patient's own preferences. However,

evidence is limited for therapeutic interventions other than clozapine and ECT for treatment-resistant schizophrenia, and most of this evidence is based on open-label studies and case reports. Even among the few randomized controlled trials (RCTs) that exist, most cannot exclude the risk of bias. Therefore, there is still no specific therapy that is understood to be highly efficacious in this area. We searched for systematic reviews and RCTs that corresponded to this CQ; however, no sufficient evidence was obtained. Thus, we created a semi-recommendation and commentary that included evidence retrieved by hand search, such as that obtained from observational studies.

In the following, we provide a commentary on our findings regarding switching to other antipsychotics, the concomitant therapy of two or more antipsychotics other than clozapine, and concomitant therapy of antipsychotics and psychotropics.

There are no RCTs that compared switching to antipsychotics (other than clozapine) with continuation of the current regimen for cases of treatment-resistant schizophrenia. There are several RCTs that compared antipsychotics other than clozapine,[1-7] and most of them compared second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs). Regarding improvements in psychiatric symptoms, there are multiple reports showing that olanzapine and risperidone were considerably superior to some FGAs,[5,6] there were no differences,[4,7] and the results were inconsistent. For improvements in quality of life (QOL), and there were no significant differences between aripiprazole and FGAs ($p = 0.052$).[3] Switching from an ineffective drug to olanzapine, risperidone, aripiprazole, perphenazine, or risperidone long-acting injections improved psychiatric symptoms, although the studies were pre- and post-group comparisons without a control group.[1,3,5,6] Regarding the increase in all-cause discontinuation the results were inconsistent in comparison to the control group. The above results suggest that switching to antipsychotics other than clozapine has an effect on treatment-resistant schizophrenia, but all these reports were small-scale, and the results varied. Thus, we propose that a switching antipsychotic other than clozapine should be done only in situations where high efficacy cannot be expected and the need for new therapeutic intervention is high, after careful consideration of the expected efficacy and likely occurrence of adverse events.

There is no reliable evidence on the efficacy of the concomitant therapy of two or more antipsychotics other than clozapine in treatment-resistant schizophrenia, but observational studies and case reports have shown that concomitant therapy of two drugs, in which some SGAs were combined, resulted in improved psychiatric symptoms.[8,9] Therefore, the efficacy of two antipsychotics other than clozapine in treatment-resistant schizophrenia has not been sufficiently verified, and further studies are needed. In term of concomitant therapy with three or more antipsychotics, there is little evidence that such therapy improves psychiatric symptoms and, it could lead to decreased drug adherence and increased adverse events from drug interactions; therefore, such an approach is not recommended.

Regarding the concomitant therapy of antipsychotics (other than clozapine) with other psychotropics, there are reports that concomitant therapy of antidepressants with antipsychotics improved psychiatric symptoms,[10,11] but these studies were conducted on a small scale and their reliability is questionable. There are also no reliable reports on the efficacy of concomitant therapy with mood stabilizers, antiepileptics, or other drugs with antipsychotics other than clozapine. Therefore, even in treatment-resistant schizophrenia, the concomitant therapy of antipsychotics (other than clozapine) with other psychotropics is not recommended.

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CHAPTER 6: OTHER CLINICAL PROBLEMS 1

CQ6-1: ARE SEDATIVE PSYCHOTROPICS RECOMMENDED FOR INSOMNIA SYMPTOMS IN PATIENTS WITH STABLE SCHIZOPHRENIA?

Semi-recommendation

Insomnia is attributed to diverse etiologies, including schizophrenia, non-schizophrenic psychiatric or physical diseases, primary sleep disorders, drugs, and the environment. Therefore, it is essential

to investigate the causes of insomnia in patients with stable schizophrenia and treat them accordingly.

Commentary

Insomnia is a frequent symptom in patients with schizophrenia[1] and causes a decrease in quality of life (QOL), requiring therapeutic interventions. However, no definitive treatment guideline has been established for managing insomnia in patients with stable schizophrenia. In clinical practice, the concomitant use of benzodiazepine receptor agonists, strong sedative antipsychotics, and strong sedative antidepressants are used to improve insomnia but their efficacy is unclear. Additionally, benzodiazepine receptor agonists have side effects such as dependence, cognitive dysfunction, and falls/fractures[2]; antipsychotics have side effects such as extrapyramidal symptoms, weight gain, and QT prolongation.[3] However, the safety of sedative psychotropics in stable schizophrenia with insomnia is uncertain. We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but no adequate evidence was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by hand searching, such as that obtained from observational studies.

In our literature search, none of the studies examined antipsychotics or antidepressants with sedating properties. Only one RCT met the PICO of this CQ,[4] which examined the benzodiazepine receptor agonist eszopiclone and included 39 subjects. In this RCT, the eszopiclone group showed significantly improved insomnia compared with the placebo group, but there were no significant differences in sleep indices as measured by sleep diaries. No significant differences were observed between the eszopiclone and placebo groups in the psychiatric symptom scale, depressive symptom scale, QOL, cognitive function, and adverse events.[4] There were no deaths, and dependence/tolerance and tardive extrapyramidal symptoms were not investigated.[4]

The systematic review of this CQ included only RCTs; therefore, the long-term benefits and harms of sedative psychotropics could not be evaluated. For benzodiazepine receptor agonists, problems such as dependence,[5] cognitive dysfunction,[6] and increased risk of falls[7] associated with long-term and high-dose use have been indicated, and some studies have also reported that long-term use of benzodiazepine receptor agonists is associated with increased mortality in patients with schizophrenia.[8] Therefore, careless long-term use should be avoided.

From the above results, taking psychotropics with sedative effects is expected to improve insomnia. However, long-term efficacy against insomnia, dependence/tolerance, and adverse events that are difficult to evaluate in a short period of time (e.g., tardive extrapyramidal symptoms) were not assessed due to the short 8-week evaluation period; rare and serious adverse events such as death could not be evaluated because of the RCT study design; the examination of sedative psychotropics other than benzodiazepine receptor agonists was lacking; and a meta-analysis was not possible due to the small number of included studies. Therefore, no recommendation was made.

Insomnia may be caused by schizophrenia, non-schizophrenic psychiatric or physical diseases, primary sleep disorders, drugs, or the environment. Therefore, a common effective treatment for insomnia with diverse etiologies has not been found. As a result, it is necessary to investigate the causes of insomnia and administer appropriate treatment strategies.

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CQ6-2: ARE AS-NEEDED ANXIOLYTICS AND SEDATIVES RECOMMENDED FOR ANXIETY, AGITATION, AND INSOMNIA IN SCHIZOPHRENIA?

Semi-recommendation

Pro re nata psychotropics with anxiolytic and sedative effects are often used for the treatment of anxiety, agitation, and insomnia in patients with schizophrenia; however, since there is insufficient evidence, their active use cannot be strongly recommended. Meanwhile, second-generation antipsychotics (SGAs) have been suggested to be effective when used as needed during periods of agitation and insomnia, and the use of pro re nata drugs that can be taken at the patient's discretion may improve quality of life (QOL). However, in CQ1-3 and CQ1-4 of this guideline, it is recommended that antipsychotics and psychotropics not be used concomitantly. There is also a risk that careless and continuous use of pro re nata drugs will lead to oversedation and high-dose polypharmacy. Therefore, even if efficacy is suggested, careless use must be avoided.

Commentary

During treatment for schizophrenia, the implementation of interventions other than regular drugs to treat anxiety, agitation, and insomnia is common. In this CQ, drugs other than regular drugs that are used for interventions are referred to as "pro re nata drugs." These are defined as "oral drugs that a medical practitioner prescribes based on an agreement with the patient, and which patients can take at their own discretion;" injection treatments are not included. Evidence on the effects of rescue drugs that were used only once was applied for evaluation. Some international guidelines recommend the selection of drugs for acute treatment. However, only the "Royal College of Psychiatrists' Guideline" in 1993 provided guidelines for "pro re nata drugs" but do not recommend specific drugs. We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but no adequate evidence was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by hand searching, such as that obtained from observational studies.

Commonly used pro re nata drugs for anxiety and agitation in schizophrenia include intravenous and intramuscular injections of first-generation antipsychotics (FGAs) or benzodiazepine receptor agonists. Even today, these drugs are sometimes used when patients are in a restless state and medical care is difficult. However, various dosage forms of SGAs have been developed. In clinical practice, SGAs have been used as pro re nata drugs needed, and there have been reports showing that these drugs were appropriate interventions. The SGA risperidone has been shown to be more beneficial than injections of FGAs even when used as a rescue drug (single use of 2 mg risperidone shows efficacy equivalent to[1] or better than[2] intramuscular injection of haloperidol and has a low occurrence of adverse events[2]). Additionally, a double-blind study comparing olanzapine and haloperidol (in both cases, oral administration of 10 mg on the first day) showed equivalent efficacy against anxiety and agitation of schizophrenia 1–24 hours after administration, and olanzapine had a superior tolerability compared with haloperidol in the subsequent period.[3] For quetiapine, an observational study of agitation in a psychiatric emergency department showed that oral administration (100–800 mg, average of 203 mg) significantly improved aggression scores (39% reduction in Overt Aggression Scale) on the first day of administration.[4] Various dosage forms that do not require water have been developed for these SGAs in recent years, such as liquid preparations (oral solutions), orally disintegrating tablets, and sublingual tablets. A domestic comparative study on the effects of a single dose of oral risperidone solution (2 mg), orally disintegrating olanzapine tablet (5 mg), and quetiapine tablets (200 mg) showed no significant difference in the Drug-induced Extrapyramidal Symptoms Scale (DIEPSS) values between before administration and 120 minutes after administration for all three drugs, and no adverse events were observed; all three groups also exhibited an improvement over time, such as a decrease in the rate of moderate or higher psychomotor agitation after 120 minutes.[5] A placebo-controlled, double-blind RCT of the recently launched asenapine sublingual tablet for acute symptoms of psychiatric disorders (39 cases of schizophrenia and schizoaffective disorder out of 120 cases) was conducted, showing rapid efficacy and safety 15 minutes after 10-mg oral administration.[6]

For mild anxiety symptoms, benzodiazepine receptor agonists are often used as pro re nata drugs in clinical practice, but there is very little evidence regarding the efficacy of oral administration of single drugs for agitation. Indeed, many clinical trials of intramuscular injection or oral administration of antipsychotics for agitation have allowed the concomitant use of benzodiazepine receptor agonists, and concomitant use may enhance the sedative effect or mitigate the side effects of antipsychotics. However, the scientific evidence is still weak. The U.S. "Expert Consensus Guideline" (2005) recommends olanzapine or risperidone monotherapy, or concomitant use of risperidone or haloperidol and a benzodiazepine receptor agonist as a first-line drug for acute symptoms of schizophrenia, and quetiapine or ziprasidone (not approved in Japan) as a second-line drug.[7] Certain advantages have been suggested for the use of pro re nata drugs for anxiety or agitation, but the possibility of continuous use of pro re nata drugs leading to high-dose polypharmacy is a disadvantage.[8] Considering that CQ1-3 and CQ1-4 of this guideline do not recommend the concomitant use of antipsychotics and psychotropics, caution must be taken to avoid the careless and continuous use of drugs for anxiety and agitation.

No placebo-controlled RCTs have examined the effects of a single-dose psychotropic for insomnia in schizophrenia. Most hypnotics have been confirmed to be useful as a single dose for patients with insomnia during their development, and if there are no significant accompanying psychiatric symptoms, then a certain efficacy may be expected for prolonged insomnia in schizophrenia. However, when insomnia is accompanied by exacerbated psychiatric symptoms, then antipsychotics are often needed. Studies investigating the effects of antipsychotics on sleep in schizophrenia, including those that have investigated the effect of polysomnography on sleep architecture, have found increases in total sleep time due to chlorpromazine,[9] increases in non-REM sleep (sleep stage 2) due to oral risperidone solutions,[10] and increases in deep slow-wave sleep due to olanzapine,[11] but the usefulness of pro re nata drugs requires further verification. Additionally, similar to anxiety and agitation, CQ1-4 of this guideline does not recommend the concomitant use of psychotropic drugs; therefore, so caution should be exercised to prevent continuous use of pro re nata drugs and a gateway for high-dose polypharmacy.

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CQ6-3: IS SWITCHING OR REDUCING ANTIPSYCHOTICS, OR REDUCING OR DISCONTINUING CONCOMITANT PSYCHOTROPICS RECOMMENDED FOR SCHIZOPHRENIA WITH HYPERSOMNIA?

Semi-recommendation

In patients with schizophrenia and hypersomnia, it is critical to differentiate between comorbidities that may cause hypersomnia and excessive sedation due to drugs other than antipsychotics. Furthermore, it is recommended to examine the influence of the antipsychotics. Concomitant use of benzodiazepine receptor agonists and antidepressants is associated with drowsiness, so consider reducing or discontinuing their use. Different antipsychotics may have different sedative effects, and if hypersomnia is believed to be caused by an antipsychotic, then switching to another with weaker sedative effects should be considered. No conclusion has been reached regarding the dose dependence of antipsychotics on sedative effects, but the possibility that dose reduction will improve hypersomnia should be investigated. These interventions also pose a risk of disease exacerbation. Thus, it is important to conduct them while comprehensively evaluating each patient's disease symptoms.

Commentary

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but no adequate evidence was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by hand searching, such as that obtained from observational studies.

For hypersomnia in schizophrenia, it is vital to first differentiate whether the symptoms are due to other pathological conditions or diseases that cause hypersomnia, drugs other than antipsychotics, or the antipsychotics themselves. Pathological conditions and diseases that cause hypersomnia include hepatic/renal dysfunction, anemia, metabolic diseases, electrolyte abnormalities, inflammatory diseases, physical diseases such as cerebral organic diseases, sleep apnea syndrome, sleep disorders with hypersomnia such as narcolepsy, and the effects of chronic sleep deprivation.[1] These conditions should first be fully differentiated from excessive sedation caused by drugs other than antipsychotics, and then the influence of the antipsychotics should be examined.[1]

For drowsiness caused by psychotropics other than antipsychotics in patients with schizophrenia, benzodiazepine receptor agonists[2] (risk ratio 3.30, 95% confidence interval [CI]: 1.04–10.40, p-value not described) and antidepressants[3] (risk ratio 3.52, 95% CI: 1.61–7.71, $p = 0.002$) have been reported to significantly increase the risk when using with antipsychotics. Therefore, although indirectly, dose reduction or discontinuation of benzodiazepine receptor agonists and antidepressants may be useful in improving hypersomnia in patients with schizophrenia. It is recommended to consider reducing or discontinuing these psychotropics.

In the pharmacological treatment of schizophrenia, the sedative effects of antipsychotics are often useful, particularly during the acute phase and relapses. Over 80% of patients in acute-phase schizophrenia have insomnia,[4] and the sedative effects of antipsychotics often improve insomnia and are useful in stabilizing the sleep–wake rhythm.[5] Furthermore, the sedative effects of antipsychotics are effective in improving agitation and excitement in the acute-phase.[6] However, in some patients, the sedative effects of antipsychotics cause hypersomnia during the maintenance treatment.[5] Prolonged symptoms of hypersomnia may contribute to decreased motivation, fatigue, difficulty concentrating, falling,[7] and weight gain,[8] and are associated with social difficulties, including those at school and work.[6] Based on the above, the sedative effects of antipsychotics should be carefully considered when using these drugs for schizophrenia.

A network meta-analysis on the sedative effect of antipsychotics for acute schizophrenia showed that over half of the antipsychotics studied produced a significant sedative effect compared with that of placebo.[9] For the use of antipsychotics for acute- and maintenance-phase schizophrenia, a meta-analysis of trials that directly compared sedation between drugs showed significantly stronger sedative effects for clozapine than for olanzapine (risk ratio 1.86, 95% CI: 1.54–2.23, $p < 0.001$), for olanzapine than for paliperidone (risk ratio 2.85, 95% CI: 1.29–6.31, $p = 0.010$), and for quetiapine than for risperidone (risk ratio 1.46, 95% CI: 1.09–1.96, $p = 0.010$).[10] Although indirectly, these findings suggest that there are differences in the degree of sedation among antipsychotics. Thus, when symptoms of hypersomnia occur in patients with schizophrenia, it is recommended to consider switching to antipsychotics with weaker sedative effects.

An RCT that compared the occurrence of hypersomnia at different doses of olanzapine in patients with acute-phase schizophrenia showed a significant correlation between the sedative effect and dose.[11] Meanwhile, a meta-analysis that compared the absolute increased risk of sedation according to antipsychotic dose showed that the correlation between sedation and

dose was unclear for many antipsychotics.[12] However, in such a meta-analysis, there are limitations, including different dose settings among studies, the difficulty in fully integrating the data, and different definitions of sedation between studies. The only study that considered the above-mentioned concerns observed a correlation between the olanzapine dose and hypersomnia[11]; therefore, the possibility of a similar dose dependency existing for other antipsychotics cannot be ruled out. Based on the above, it is recommended that a reduction in antipsychotics be considered for the possibility of improving hypersomnia.

Thus, to improve hypersomnia in patients with schizophrenia, it is recommended to consider interventions such as dose reduction or discontinuation of benzodiazepine receptor agonists and antidepressants, switching from antipsychotics with strong sedative effects to those with weak sedative effects, and antipsychotic dose reduction. However, discontinuation of antipsychotics is a risk factor for relapse,[13] thus emphasizing the importance of considering the potential exacerbation of psychotic symptoms due to switching the antipsychotic or reducing its dose (see CQ2-1 and CQ2-2). Withdrawal symptoms when discontinuing benzodiazepine receptor agonists and antidepressants should also be considered.[14,15] It is important to conduct these interventions while comprehensively considering the conditions of individual patients.

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CQ6-4: WHAT PHARMACOLOGICAL TREATMENT IS USEFUL FOR DEPRESSIVE SYMPTOMS OF SCHIZOPHRENIA?

Semi-recommendation

It is necessary to understand that there are various causes of depressive symptoms of schizophrenia and to respond accordingly.

Antipsychotics improve depressive symptoms, psychiatric symptoms, and quality of life (QOL) in schizophrenia. Meanwhile, weight gain, elevated prolactin levels, QTc interval prolongation, increased use of antiparkinsonian drugs, and increased occurrence of sedation are observed with antipsychotic use. Based on the above, when considering efficacy and safety, antipsychotic treatment is recommended for depressive symptoms of schizophrenia.

Antipsychotic dose reduction does not improve depressive symptoms, and there were no differences in discontinuation due to adverse events, exacerbation of overall psychiatric symptoms, QOL, and suicide attempts. Based on the above, when considering efficacy and safety, dose reduction of antipsychotics to improve depressive symptoms in schizophrenia is not recommended.

In cases of concomitant use of antipsychotics with antidepressants, QOL has been reported to improve, but no improvements in depressive symptoms were observed, there were no differences compared with antipsychotics treatment only in discontinuation due to adverse events and in exacerbation of psychotic symptoms, and the occurrence of dry mouth increased. Based on the above, when considering efficacy and safety, the concomitant use of antidepressants for improving depressive symptoms in schizophrenia is not recommended.

Commentary

Depressive symptoms of schizophrenia occur in all stages, such as the prodromal stage, initial onset, acute stage, after psychosis in the recovery stage, and before relapse in the chronic stage.[1] The prevalence of depressive symptoms is 6–75%, with a mode of 25%.[2] Comorbid depressive symptoms lead to difficulties in social life and an increased risk of suicide.[3,4]

The etiology is extremely complex and should be differentiated while considering the side effects of antipsychotics, drug abuse and withdrawal, the disease itself, psychological reactions to social difficulties, and facility-related aspects such as long-term hospitalization.[5] Therefore, it is necessary to understand that the depressive symptoms of schizophrenia have various etiologies, and to take measures according to the etiology.

We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but no adequate evidence based on direct comparisons was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by hand searching, such as that obtained from observational studies, using network meta-analyses. A network meta-analysis of RCTs evaluating the effects of antipsychotics on depressive symptoms in schizophrenia (N [number of studies] = 89, n [number of patients] = 19 683)[6] showed that 10 out of 14 antipsychotics approved in Japan reduced depressive symptoms compared with a placebo, but the other four drugs (zotepine, perphenazine, pimozide, and chlorpromazine) showed no significant differences. As described in CQ1-1, antipsychotic treatment improved overall psychiatric symptoms, positive symptoms, and QOL, but also increased adverse events resulted in weight gain, elevated prolactin levels, QTc interval prolongation, increased use of anti-parkinsonian drugs, increased occurrence of sedation.[7] There were no reports on evidence related to suicide. Based on the above, when considering efficacy and safety, antipsychotic treatment is recommended for depressive symptoms of schizophrenia.

None of the four RCTs that evaluated improvements in depressive symptoms by reducing antipsychotic dose[8-11] showed a significant difference in depressive symptom improvements between the antipsychotic dose-reduction group and non-reduction group. Furthermore, as described in CQ2-2, a recent meta-analysis of 18 RCTs ($n = 1385$) comparing antipsychotic dose reduction and dose maintenance[12] showed that there were no significant differences in terms of discontinuation due to adverse events, exacerbation of overall psychiatric symptoms, and QOL improvement (see CQ2-2 for details). One RCT ($n = 97$) reported on suicide attempts between the dose-reduction group and non-reduction group, but no significant differences were observed.[8] Based on the above, when considering efficacy and safety, reducing the dose of antipsychotics for depressive symptoms of schizophrenia is not recommended.

A meta-analysis of RCTs that evaluated depressive symptoms following the concomitant use of either antidepressants or a placebo during antipsychotic treatment ($N = 25$, $n = 1129$)[13] showed that concomitant antidepressant treatment did not have a significant antidepressant effect. No significant difference was detected in discontinuation due to adverse events between the concomitant antidepressant treatment group and the non-concomitant group ($N = 37$, $n = 664$); however, research on other side effects ($N = 3$, $n = 140$) indicated that the concomitant use of antidepressants considerably increased the occurrence of dry mouth. Regarding the exacerbation of psychotic symptoms ($N = 8$, $n = 379$), no significant difference was observed between the concomitant antidepressant group and placebo group, whereas QOL improved with the concomitant use of antidepressants ($N = 5$, $n = 405$). There were no clear reports on evidence related to suicide. In this meta-analysis, the concomitant use of antidepressants improved overall symptoms of schizophrenia ($N = 30$, $n = 1311$) and negative symptoms ($N = 32$, $n = 1348$), indicating that the concomitant use of antidepressants may improve symptoms other than depression. However, in this CQ, the most important outcome is the effect on depressive symptoms, and the use of antidepressants for symptoms other than depressive symptoms is considered off-label use. Thus, the concomitant use of antidepressants is not recommended.

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CQ6-5: IS THERE PHARMACOLOGICAL TREATMENT RECOMMENDED FOR COGNITIVE DYSFUNCTION OF SCHIZOPHRENIA?

Recommendation

Second-generation antipsychotics (SGAs) improve cognitive dysfunction in schizophrenia more than first-generation antipsychotics (FGAs) (B). Compared with FGAs, SGAs showed no difference in

all-cause discontinuation (B) but had fewer relapses (B) and fewer rehospitalizations (B). The concomitant use of other drugs, including anticholinergics and benzodiazepine receptor agonists, did not improve cognitive dysfunction (D).

Based on this evidence, when considering efficacy and safety, it is recommended that SGAs be used for cognitive dysfunction in schizophrenia and that concomitant use of other drugs such as anticholinergics and benzodiazepine receptor agonists is not recommended (1B).

Commentary

Cognitive function refers to comprehensive abilities such as memory, thinking, comprehension, calculation, learning, language, and judgment[1,2] Cognitive dysfunction in schizophrenia is thought to be a core symptom of the disease that is independent of other psychiatric symptoms, and its improvement is strongly related to improvements in social function and functional outcomes,[2,3] emphasizing its importance. Cognitive dysfunction reportedly occurs in many schizophrenic patients (50%–80%), but caution is advised as this symptom is not seen in all cases.[4] Different studies use different evaluation scales for cognitive dysfunction in schizophrenia, and neuropsychological tests such as the Brief Assessment of Cognition in Schizophrenia (BACS) and the Wechsler Adult Intelligence Scale (WAIS) are both used, which can complicate interpretation.[5]

In general, long-term concomitant use of anticholinergics and benzodiazepine receptor agonists exacerbates cognitive dysfunction.[6-8] Therefore, as already indicated in the 2017 revision of the Guideline for Pharmacological Therapy of Schizophrenia, "CQ5-4: Is there a recommended pharmacological treatment for cognitive dysfunction in schizophrenia?" concomitant use of anticholinergics and benzodiazepine receptor agonists should be avoided since they adversely affect cognitive function.

Owing to the prevailing assumption that antipsychotic treatment is a fundamental component of schizophrenia treatment, there is a scarcity of placebo-controlled studies focusing on the amelioration of cognitive dysfunction. Although a few studies on antipsychotics with a placebo control have reported improvement in cognitive dysfunction, the effects of antipsychotics on cognitive dysfunction should be examined by considering the actual clinical circumstances. Therefore, in this CQ, we will mainly explain the contents of these studies examined through the comparison of SGAs and FGAs.

SGAs are more effective in improving cognitive dysfunction than FGAs, but the improvement effect size was small, at approximately 0.24 (N [number of studies] = 14, n [number of patients] = 514, Hedges' $g = 0.24$, 95% confidence interval [CI]: 0.11–0.37)[9] (B). Such an improvement effect on cognitive dysfunction was also observed when the cases were limited to first-episode psychosis, including short-term psychotic disorder ($N = 11$, $n = 1932$, Hedges' $g = 0.25$, 95% CI: 0.10–0.40).[10] Comparisons between SGAs can only be made by network meta-analysis, but according to this study, the results of improvements in cognitive dysfunction among SGAs are inconsistent among studies.[11,12]

No studies have evaluated psychiatric symptoms, adverse events, and treatment discontinuation concurrently with cognitive function improvement effects in schizophrenia. However, as mentioned above in CQ2-4 of this guideline, for the maintenance treatment of schizophrenia, although no differences in all-cause discontinuation were found between SGAs and FGAs, the former had fewer relapses and rehospitalizations.[13] Therefore, it is recommended that SGAs are used rather than FGAs.

Evidence for concomitant treatment of psychotropics other than antipsychotics is limited. There is scarce evidence related to improvements in cognitive function due to the concomitant use of other drugs (memantine, minocycline, cholinesterase inhibitors, antidepressants, azapirone anxiolytics, atomoxetine, amphetamine, methylphenidate, pregnenolone, erythropoietin, oxytocin, lamotrigine, modafinil, and varenicline) (D).

Based on this evidence, when considering efficacy and safety, it is recommended that SGAs are used for cognitive dysfunction in schizophrenia and that concomitant use of other drugs such as anticholinergics and benzodiazepine receptor agonists is not recommended (1B).

Psychosocial treatment plays a crucial role in cognitive dysfunction in schizophrenia, and this is described in Chapter 2 "Overview of schizophrenia treatment" in Part 1 "Creation of schizophrenia treatment plan," so please refer to this.

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CHAPTER 7: OTHER CLINICAL PROBLEMS 2

CQ7-1: WHAT PHARMACOLOGICAL TREATMENT IS RECOMMENDED FOR PSYCHOMOTOR AGITATION?

Recommendation

Oral antipsychotics are reportedly effective for psychomotor agitation in schizophrenia (D). No significant differences were detected in the effect on psychomotor agitation between drugs (C); however, oral second-generation antipsychotics (SGAs) were better tolerated than oral haloperidol in terms of extrapyramidal symptoms (D). Based on the above, in the case of oral administration, pharmacological treatment with SGAs is suggested (2D). With regard to intramuscular preparations, olanzapine and haloperidol intramuscular injections were more effective than placebo (C). Haloperidol intramuscular injections reportedly cause extrapyramidal symptoms (C); therefore, olanzapine intramuscular injections are suggested (2C).

No differences were observed in the improvement in psychomotor agitation between oral and intramuscular administration (D). Based on the above, it is recommended to establish effective communication with the patient and to prioritize oral administration (1D).

Commentary

Patients with schizophrenia may exhibit acute behavioral disturbance as psychotic symptoms, and they may develop secondary aggression toward others due to persecutory delusions, auditory hallucinations, and visual hallucinations. For acute behavioral disturbance, as a rule, it is essential to undertake an appropriate psychological and behavioral approach first, combined with appropriate oral administration. If oral administration is not possible, then rapid sedation is conducted by intramuscular or intravenous administration.[1]

Some placebo-controlled studies have been published that support the efficacy of oral antipsychotics (haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, and asenapine) in psychomotor agitation[2-15] (D), but no clear difference was detected between the drugs in improving psychomotor agitation (C). It has been reported that SGAs have fewer adverse events such as extrapyramidal symptoms than haloperidol, which is a representative first-generation antipsychotic (D). However, in all studies, the level of behavioral disturbance in the enrolled patients remained at a moderate level, the subjects were administered SGAs as monotherapy, and efficacy or safety when added as a rescue drug was not verified. Therefore, the oral administration of SGAs is suggested (2D).

For intramuscular injections, some studies have been published to support the efficacy of intramuscular olanzapine compared with a placebo[16-21] (C), and other studies have been published to support the efficacy of intramuscular haloperidol compared with a placebo[19,22] (C). Two studies compared olanzapine and haloperidol, and olanzapine and haloperidol + lorazepam,[20,21] but neither reported significant differences in efficacy (C). For side effects, a comparative study of olanzapine, haloperidol, and a placebo reported significant QT prolongation in the haloperidol administration group[23] (C).

Evidence for the concomitant use of antipsychotics and psychotropics includes several studies on the concomitant use of intramuscular injections of haloperidol and promethazine. According to these reports, when compared with the concomitant use of these two drugs, haloperidol monotherapy was less effective and less tolerable[24] (D), midazolam monotherapy produced a faster sedative effect[25] (C), it took longer for lorazepam monotherapy to achieve a sedative effect[26] (C), and olanzapine intramuscular injections had approximately the same level of efficacy, but the sustained effect may have been longer with intramuscular injections of haloperidol and promethazine[27] (C). However, the National Institute for Health and Care Excellence (NICE) in the United Kingdom has questioned the evidence for intramuscular promethazine injections.[28]

A comparison of oral and intramuscular administrations of antipsychotics showed no significant difference in the improvement in psychomotor agitation[4,5] (C). No reliable evidence has been obtained for comparisons with other administrations, including intravenous administration, and no reports have been identified at this time examining what order of administration would be effective.

In addition to improvements in psychomotor agitation, important outcomes also include reductions in mortality and improvements in quality of life (QOL). However, no clear evidence has been obtained for these outcomes, and only a small number of adverse events (except death) have been reported; only those that were reported are described.

Based on the above, it is recommended to communicate with the patient as much as possible and to prioritize oral administration (1D).

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CQ7-2: WHAT TREATMENT IS RECOMMENDED FOR CATATONIA OF SCHIZOPHRENIA?

Semi-recommendation

There is insufficient evidence regarding the efficacy and safety of antipsychotics for catatonia in schizophrenia. Therefore, it is preferable to conduct a comprehensive differential diagnosis, closely monitor the patient's overall condition, and administer pharmacological treatment in accordance with standard treatment protocols for schizophrenia. If malignant syndrome is suspected, then treatment should be initiated immediately.

The efficacy of electroconvulsive therapy (ECT) and benzodiazepine receptor agonists has been reported for catatonic symptoms associated with various diseases, not just schizophrenia. It is recommended to consider ECT and benzodiazepine receptor agonists, but their safety should be taken into consideration.

Commentary

According to DSM-5, the essential feature of catatonia is a pronounced psychomotor disturbance. Catatonia has a complex presentation ranging from pronounced decline in mental activity (e.g., so-called stupor) to motor stereotypies and pathological hyperactivity such as agitation that is not induced by external stimuli. Catatonia is divided into disturbances related to other psychiatric disorders, including schizophrenia; those related to other medical disorders; and those that are unspecified.[1]

When examining the pathological condition of catatonia, regardless of the presence or absence of a history of schizophrenia, it is necessary to first search for the cause, assuming that various organic factors such as infectious (e.g., encephalitis), neurological, endocrine, and metabolic diseases could be contributing factors. Recent research

has indicated a relationship with the immune system, including autoimmune encephalitis.[2] Catatonia can lead to life-threatening physical diseases such as deep vein thrombosis and pulmonary embolism. Hospitalization is often required, with interventions to improve dehydration and malnutrition (e.g., tube nutrition and parenteral nutrition) being necessary.[3] Differentiation from malignant syndrome is also important, and suspected cases should be treated immediately. The deteriorating general condition of the patient can lead to long-term bed rest, which is highly likely to reduce quality of life (QOL) due to disuse syndrome. Therefore, the prompt diagnosis and treatment of catatonia are important to prevent the risk of death and QOL deterioration. We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but no adequate evidence was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies.

There were no RCTs on the efficacy of antipsychotics for catatonia in schizophrenia, but a review on catatonia showed that first-generation antipsychotics (FGAs) are often ineffective and may exacerbate catatonic symptoms.[4] Therefore, caution should be exercised when selecting FGAs as pharmacological treatment for catatonia. Additionally, no consensus has been reached for second-generation antipsychotics (SGAs). However, clozapine, olanzapine, risperidone, quetiapine, aripiprazole, etc. have been reported to be effective for patients who are catatonic and in whom symptoms have not improved with benzodiazepine receptor agonists, but SGAs may also exacerbate catatonic symptoms and malignant syndrome, so caution is warranted.[5] It has also been indicated that neuroleptic-induced catatonia (NIC) induced by antipsychotic treatment may be an early symptom of malignant syndrome.[6] A clinical trial in which lorazepam was administered to 50 schizophrenia patients with catatonia and ECT or oral psychotropic drugs were administered to those who did not respond to lorazepam treatment indicated only a 2% improvement with benzodiazepine receptor agonists, as opposed to 68%, 26%, and 16% improvement with the antipsychotics chlorpromazine, risperidone, and haloperidol, respectively, showing the relatively high efficacy of antipsychotics.[7] There is very weak evidence that antipsychotic treatment improves catatonic symptoms, but it is advisable to carefully differentiate whether the catatonia arises from schizophrenia or represents the early symptoms of malignant syndrome, such as NIC caused by antipsychotics. Pharmacological treatment should then be administered, while considering the patient's general condition.

For ECT, a meta-analysis on the efficacy of ECT for catatonia in schizophrenia and other psychiatric disorders (*N* [number of studies] = 28, *n* [number of patients] = 564) showed significant improvements in catatonic symptoms.[8] Additionally, a review of schizophrenia with catatonia during the maintenance period indicated that catatonic symptoms reappeared in many patients in the maintenance phase who had undergone ECT,[5] whereas another study reported that ECT maintenance treatment reduced the relapse rate in 11 schizophrenia patients with catatonia that exhibited remission with ECT.[9] Adverse events such as arrhythmia during ECT and memory impairment after ECT were reported in the above-mentioned meta-analysis, and attention should be given to the possibility of an increase in ECT-specific adverse events.[8] ECT improves catatonic symptoms and is effective for catatonia in schizophrenia, but it may increase adverse events, so the safety of introducing ECT in catatonia should be carefully considered.

For lorazepam, an RCT indicated no significant difference in symptom improvement before and after drug administration for chronic schizophrenia with catatonia,[10] but in a case series, remission was observed for acute catatonia.[11] A review of the literature on observational studies of schizophrenia with catatonia showed that lorazepam was the most used drug, with a common dosage of 8–24 mg/day.[5] Based on the above, benzodiazepine receptor agonists may improve catatonic symptoms in schizophrenia, so their use should be considered for the treatment of catatonia in schizophrenia. There is limited evidence regarding efficacy for the other agents, and their use is discouraged.

All catatonic disorders, including catatonia in schizophrenia, are pathological conditions that reduce patient QOL and can be life-threatening. There is insufficient evidence for treatments despite the need for immediacy, and there is currently no recommended treatment. In the future, it is hoped that the pathophysiology of catatonia will be further elucidated and that evidence supporting its treatment will be accumulated.

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CQ7-3: WHAT PHARMACOLOGICAL TREATMENT IS RECOMMENDED FOR PATHOLOGICAL POLYDIPSIA AND WATER INTOXICATION?

Semi-recommendation

Second-generation antipsychotics (SGAs) may be effective as antipsychotic treatments for pathological polydipsia; therefore, it is recommended to administer standard pharmacological treatment with SGAs appropriately. Clozapine should be introduced if pathological polydipsia is believed to be related to the pathology of treatment-resistant schizophrenia. There are no recommended pharmacological treatments involving psychotropics, other than antipsychotics.

Commentary

It has been reported that 10–20% of patients in psychiatric hospitals in Japan suffer from polydipsia, and 3%–4% suffer from water intoxication.[1] A similar frequency has been reported in Europe and the United States.[2] Hyponatremia due to water intoxication can lead to heart failure, disturbance of consciousness, convulsions, rhabdomyolysis, malignant syndrome,[3] and shortened life expectancy.[4] Therefore, countermeasures against pathological polydipsia are clinically important, but there are few large-scale prospective studies. Additionally, many of the reports on individual efforts focus on interventions in the treatment environment and behavioral patterns, and there are few reports that focus on pharmacological treatment, with the level of evidence being low. We searched for systematic reviews and randomized controlled trials (RCTs) that corresponded to this CQ, but no adequate evidence was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies.

We examined antipsychotics that are useful for pathological polydipsia using a recent systematic review of one double-blind RCT, four single-arm studies, one cross-sectional study, three case series, and 52 case reports.[5] The double-blind RCT found no significant difference in improvement between olanzapine and haloperidol. Two of the single-arm studies suggested an effect of clozapine, whereas risperidone was ineffective in the remaining two single-arm studies. The cross-sectional study showed that the frequency of hyponatremia was 26.1% for first-generation antipsychotics, 3.4% for clozapine, and 4.9% for other SGAs, indicating a low risk for SGAs. The two case series suggested an effect of clozapine. Several studies have indicated that clozapine treatment is effective. There are reports that replacement with SGAs was effective, but the evaluation was not consistent. Pathological polydipsia and water intoxication were reported before the advent of antipsychotics, and these disorders may be considered part of the psychiatric symptoms of schizophrenia. Therefore, it is recommended to appropriately administer standard pharmacological treatment with SGAs. Next, when pathological polydipsia/water intoxication is serious and considered to be caused by symptoms of treatment-resistant schizophrenia; then, the introduction of clozapine should be considered.

Next, we investigated other psychotropics that are useful for pathological polydipsia. There were two very small-scale, placebo-controlled double-blind RCTs that investigated the efficacy and safety of the antibiotic demeclocycline and opioid antagonist naloxone, but no significant information was obtained in either study.[6] The therapeutic effects of angiotensin-converting enzyme inhibitors, β-blockers, opioid antagonists, demeclocycline, carbamazepine, and lithium have been reported, but the number of cases was small, and evaluations were inconsistent.[6] Furthermore, the risk of side effects due to concomitant use is unclear, so no pharmacological treatments are currently recommended.

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CQ7-4: ARE ANTIPSYCHOTICS USEFUL FOR SCHIZOPHRENIA DURING PREGNANCY?

Semi-recommendation

Antipsychotic treatment of schizophrenia during pregnancy appears to reduce relapses and hospitalization.

Adverse events in the patient and neonatal maladjustment syndrome in the newborn may increase. However, in general, neonatal maladaptation syndrome is often treated successfully by symptomatic treatment alone, and there are no increased risks of adverse fetal events and no risks of neurodevelopmental delay in infants, so it is recommended to implement antipsychotic treatment.

Commentary

Pregnancy in patients with schizophrenia can be worrisome for the patient, her family, and even her healthcare provider. Comprehensive clinical questions such as “how will my condition change with pregnancy?”, “is it safe to continue taking antipsychotics during pregnancy?”, and “is there any effect on the fetus” easily come to mind. However, even if clinical research on these questions is attempted, conducting a high-quality randomized controlled trial (RCT) is difficult. The quality of evidence from the few observational studies that exist is not sufficiently high. Therefore, we searched for systematic reviews and RCTs that corresponded to this CQ, but no adequate evidence was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies. Additionally, the “Perinatal Mental Health Consensus Guide 2017”[1] and “Guideline for Obstetric

and Gynecological Practice–Obstetrics (2017)"[2] should be referenced since explanations to patients and families, measures other than pharmacological treatment, measures for gestational diabetes, and cooperation with other healthcare providers are also mentioned.

Although there are no reliable studies of maternal relapse or maternal hospitalization following antipsychotic treatment specifically for schizophrenia during pregnancy, antipsychotic treatment has been shown to reduce relapse and hospitalization in schizophrenia in general (see CQ2-1), and the same can be considered for schizophrenia during pregnancy.

A search for adverse events of antipsychotic treatment for schizophrenia during pregnancy showed that there were no studies limited to patients with schizophrenia; the majority of studies focused on the onset of gestational diabetes due to exposure to antipsychotics during pregnancy, so we investigated these studies. A meta-analysis of the National Institute for Health and Care Excellence (NICE) "NICE Guideline 2018" (N [number of studies] = 3, antipsychotic-exposure group n [number of patients] = 1397, non-exposure group $n = 1\,316\,979$) showed that antipsychotic administration was significantly associated with an increased risk of gestational diabetes (odds ratio 2.32, 95% confidence interval [CI]: 1.53–3.52), but there were no meta-analyses that were limited to schizophrenia.[3] Two studies published after the "NICE Guideline 2018" and by the time of our literature search found that exposure to second-generation antipsychotics (SGAs) was not associated with the development of gestational diabetes mellitus.[4,5] Drug-specific studies found no increased risk of gestational diabetes with the use of aripiprazole or risperidone,[6,7] but increased risk was found with the use of olanzapine (risk ratio 1.61, 95% CI: 1.13–2.29) and quetiapine (risk ratio 1.28, 95% CI: 1.01–1.62).[7] Thus, the use of antipsychotics may increase the occurrence of gestational diabetes.

Neonatal maladaptation syndrome occurs when drugs taken by women during pregnancy pass through the placenta to the fetus. This syndrome causes tremors, lethargy, decreased or increased muscle tone, convulsions, irritability, respiratory abnormalities, diarrhea, vomiting, and poor feeding in newborns. No studies on neonatal maladaptation syndrome have examined the use of antipsychotics in patients with schizophrenia or psychiatric disorders. Some studies suggest that neonatal maladaptation syndrome occurs more frequently in antipsychotic-exposure groups than in non-exposure groups. In one study, the polypharmacy group (including other psychotropics) may have had a higher occurrence, but no differences were observed between the antipsychotic monotherapy group and the non-exposure group.[8] In general, neonatal maladaptation syndrome is often cured by symptomatic treatment alone. Therefore, it is essential for the overseeing healthcare provider to notify the birth facility that the mother is taking the drug, and the birth facility receiving the notification should carefully monitor the condition of the infant after delivery. Based on the above, it is believed that there is no prophylactic need to discontinue antipsychotics. The general occurrence of congenital malformation, which is a fetal adverse event, varies depending on the literature, with a value of approximately 3%–5%.[2] For the relationship between antipsychotic exposure during pregnancy (not limited to studies on schizophrenia) and risk of congenital malformations, early exposure to first-generation antipsychotics or SGAs during pregnancy did not increase the risk of major congenital malformations or cardiac malformations compared with that of unexposed pregnancies.[9] The proportion of babies who were small for their gestational age did not change in women who were pregnant and exposed to antipsychotics,[3] nor was there an increased risk of premature birth.[3,5] Based on the above, for cases of schizophrenia during pregnancy, there is no evidence that antipsychotics increase the risk of fetal adverse events such as congenital major malformations, increase the number of babies that are small for their gestational age, and increase the occurrence of premature births. For the effects of antipsychotic use on neurodevelopment of the offspring in cases of schizophrenia during pregnancy, a report indicated no statistically significant difference between the antipsychotics-exposure group ($n = 76$) and the non-exposure group ($n = 76$) in the mean score of developmental tests and rate of developmental delay at 52 weeks of age.[10]

Thus, it is recommended to conduct antipsychotic treatment for schizophrenia during pregnancy.

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CQ7-5: ARE ANTIPSYCHOTICS USEFUL FOR WOMEN WITH SCHIZOPHRENIA IN POSTPARTUM PERIOD (INCLUDING THOSE WHO ARE BREASTFEEDING)?

Semi-recommendation

Antipsychotic treatment in women with schizophrenia in the postpartum period (including those who are breastfeeding) appears to reduce relapses and hospitalization. Breastfeeding while taking antipsychotics is also unlikely to affect the baby. Therefore, it is preferred that antipsychotic treatment be conducted for women with schizophrenia in the postpartum period (including those who are breastfeeding).

Commentary

The first concern of patients with schizophrenia, their families, and their healthcare providers in charge after childbirth is the possibility of breastfeeding. There have been various situations encountered in practice, such as patients who had an extremely strong desire to breastfeed and stopped oral medication due to concerns about effects on the newborn, which resulted in relapse, or those who stopped breastfeeding reluctantly because they were told that they should not breastfeed while taking medication. However, it is difficult to conduct randomized controlled trials (RCTs) for this clinical question and even with available observational studies, there is little sufficient evidence. This remains a clinical question that is currently difficult to evaluate. Therefore, we searched for systematic reviews and RCTs that corresponded to this CQ, but no adequate evidence was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies. Additionally, the "Perinatal Mental Health Consensus Guide 2017"[1] should be referenced when using this CQ because explanations to patients and families, measures other than pharmacological treatment, and cooperation with other healthcare providers are also mentioned.

There were no reliable studies of maternal relapse and maternal hospitalization with antipsychotic treatment specifically for schizophrenia during pregnancy, but antipsychotic treatment has been shown to reduce relapse and hospitalization in patients with schizophrenia (see CQ2-1).

Antipsychotics are secreted into breast milk, thereby exposing infants to the drugs through breast milk. The relative infant dose is an indicator of the amount of drug intake by infants through breast milk. It represents the percentage of the total amount of drug ingested by infants through breast milk (mg/kg/day) relative to the usual dose of the drug administered to infants (mg/kg/day). If the usual infant dose is not determined, then the therapeutic dose per mother's body weight is used. The "Guideline for Obstetric and Gynecological Practice–Obstetrics" states that, "depending on the type of drug, if the relative infant dose is well below 10%, then the effect on the infant is estimated to be small. Meanwhile, if the relative infant dose greatly exceeds 10%, then considerable caution is required".[2]

A review of second-generation antipsychotics (SGAs) and breastfeeding showed that the relative infant dose was approximately 1.6% for olanzapine, less than 1% for quetiapine, and approximately 3.6% for risperidone. Partly due to the small number of cases, aripiprazole had a range of 0.7–8.3%, but all SGAs had values of less than 10%.[3] Additionally, no serious side effects have been reported in infants, so oral administration of antipsychotics and breastfeeding are thought to be compatible. The "Perinatal Mental Health Consensus Guide 2017" states that, "if the mother has a strong desire to breastfeed and the baby has adequate excretory and metabolic function, then it is not necessary to actively stop breastfeeding for most of the drugs used to treat mental disorders".[1] However, case reports of somnolence, irritability, and poor weight gain in infants are common. Thus, when mothers taking antipsychotics breastfeed, they should pay attention to how the infant drinks, how he/she sleeps, his/her mood, and his/her weight gain, and patients should be instructed to report any abnormalities in these aspects to the healthcare provider in charge. We were unable to find any studies that examined whether antipsychotics improve infant health during the postpartum period in women with schizophrenia, increase delays in infant development, reduce maternal abuse, or improve motherhood. However, as mentioned above, for SGAs and breastfeeding, the relative infant dose for any drug was less than 10%, and there have been no reports of serious side effects in infants, so the possibility of effects on infants is believed to be low.

Schizophrenia relapse is thought to have a large impact on patients and child-rearing, and infants are unlikely to be impacted by breastfeeding while the mother takes antipsychotics. Therefore, women with schizophrenia in the postpartum period (including those who are breastfeeding) should be treated with antipsychotics.

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CQ7-6: ARE ANTIPSYCHOTICS USEFUL FOR FIRST-EPISODE PSYCHOSIS?

Semi-recommendation

Antipsychotic treatment in the acute-phase of first-episode psychosis improves psychiatric symptoms in more than 80% of patients. Therefore, antipsychotic treatment is recommended in acute-phase treatment of patients with first-episode psychosis. There were no significant differences in the improvement of overall psychiatric symptoms and all-cause discontinuation between antipsychotics.

Patients with remitted/stable first-episode psychosis after antipsychotic treatment were at higher risk of relapse from 2 months to 2 years after antipsychotic discontinuation, but no differences were detected in all-cause discontinuation, psychiatric symptoms, or quality of life between antipsychotic discontinuation and continuation. Rehospitalization rates were higher with discontinuation for a period of at least 5 years, and mortality increased when antipsychotics were discontinued immediately after initial discharge from the hospital and within 1 year. Based on the above, it is recommended to

continue antipsychotic treatment for at least 2 years in patients with remitted/stable first-episode psychosis, but there are many patients who do not relapse even after discontinuation, so the patient and physician should conduct shared decision-making (SDM) regarding whether the discontinuation of treatment is appropriate.

Commentary

First-episode psychosis is the first manifestation of psychiatric symptoms such as hallucinations, delusions, agitation, stupor, catatonic symptoms, and pronounced behavioral disturbance. The clinical studies of first-episode psychosis were problematic in that schizophrenia, schizoaffective disorder, delusional disorder, schizophreniform disorder, short-term psychotic disorder, etc., were not differentiated and were collectively classified as first-episode psychosis. This is believed to be caused by the fact that differentiating between the above diseases is often difficult in actual clinical settings, and there is often no choice but to intervene in the acute-phase due to the severity of psychiatric symptoms without differentiating them. Furthermore, another aspect that makes clinical studies on first-episode psychosis difficult is the question of whether to continue antipsychotics. There are advantages and disadvantages to the continuous antipsychotics for patients with remitted/stable first-episode psychosis after antipsychotic treatment, or do not have symptoms that satisfy the diagnosis of other psychiatric disorders. The continuation of antipsychotic treatment may be necessary in the case of schizophrenia but is not essential for patients who do not have schizophrenia. The continuation of treatment sometimes imposes safety concerns and financial burdens on patients and their families.

In fact, a literature search on first-episode psychosis revealed that there were no randomized controlled trials (RCTs) that compared antipsychotics and placebos in the acute-phase, perhaps reflecting actual clinical circumstances, with only comparative studies between psychotropics found. There were RCTs comparing antipsychotic continuation with a placebo for patients with remitted/stable first-episode psychosis after antipsychotic treatment. We searched for systematic reviews and RCTs that corresponded to this CQ, but no adequate evidence was available. Thus, we created a semi-recommendation and commentary that included evidence retrieved by manual searching, such as that obtained from observational studies.

A single-group meta-analysis showed that 81.3% of patients with first-episode psychosis had improvements in psychiatric symptoms due to antipsychotic treatment relative to baseline[1] (N [number of studies] = 17, n [number of patients] = 3156). Although direct comparisons cannot be definitively established, this treatment response rate may be higher than the response rate for schizophrenia[2] (51%). A network meta-analysis investigated the efficacy and tolerability of 12 types of antipsychotics for the acute-phase treatment of patients with first-episode psychosis[3] ($N = 19$, $n = 2669$). Focusing on the drugs approved in Japan, olanzapine and risperidone were superior to haloperidol in the improvement of overall psychiatric symptoms, and there were no significant differences between the other drugs. Aripiprazole, quetiapine, risperidone, and olanzapine were superior to haloperidol in all-cause discontinuation, but there were no significant differences between the other antipsychotics. Therefore, it is recommended to conduct antipsychotic treatment, and it may be preferred over haloperidol for some second-generation antipsychotics.

A meta-analysis of RCTs that compared relapse rates between antipsychotic treatment maintenance and discontinuation groups in patients with first-episode psychosis who were in remission or were stable following antipsychotic treatment[4] ($N = 10$, $n = 739$) showed that the relapse rate was higher in the group where 12 months had passed since antipsychotic discontinuation than in the group that maintained antipsychotic administration during that period [discontinuation group 54.3%, maintenance group 24.0%, number needed to treat = 3]. Subgroup analysis showed that the difference in relapse rate was statistically significant from 2 months after antipsychotic discontinuation up to at least 2 years (24 months) after discontinuation (2 months: discontinuation group 13.0%, maintenance group 5.8%, number needed to treat = 13; 18–24 months: discontinuation group 60.6%, maintenance group 34.6%, number needed to treat = 4). Based on the above, discontinuing antipsychotics for at least 2 months in patients with remitted/stable first-episode psychosis after antipsychotic treatment significantly increased the risk of relapse, and the difference in risk was consistent until at least 2 years (24 months) after discontinuation. There were no significant differences between the antipsychotic treatment discontinuation and maintenance groups of patients with first-episode psychosis in terms of all-cause discontinuation ($N = 7$, $n = 636$) and exacerbation of psychiatric symptoms and QOL ($N = 2$, $n = 175$).[4]

A 20-year cohort study of patients in Finland with first-episode psychosis ($n = 8179$) compared the rehospitalization rates between the antipsychotic treatment maintenance and discontinuation groups, with patients divided into five drug discontinuation periods.[5] The rehospitalization rate in each period was as follows: (1) immediately after discharge following initial hospitalization: discontinuation group 51.4%, maintenance group 32.7%. (2) Less than 1 year: discontinuation group 41.2%, maintenance group 28.9%. (3) From 1 year to less than 2 years: discontinuation group 31.0%, maintenance group 28.9%. (4) From 2 years to less than 5 years: discontinuation group 27.7%, maintenance group 23.4%. (5) Five or more years (7.9 years on average): discontinuation group 24.1%, maintenance group 19.7%. Compared with the antipsychotic treatment maintenance group, the discontinuation group had a significantly higher rehospitalization rate for all periods. Compared with the antipsychotic treatment maintenance group (1.5%), the group that discontinued antipsychotic treatment immediately after discharge following initial hospitalization (4.8%) and for less than 1 year (2.6%) had significantly higher mortality rates. Meanwhile, the mortality rates were 1.1% for the group that discontinued from 1 year to less than 2 years, and 3.9% for the corresponding maintenance group; 1.5% for the group that discontinued from 2 years to less than 5 years, and 2.9% for the corresponding maintenance group; and 1.5% for the group that discontinued after 5 years (7.9 years on average), and 0% for the corresponding maintenance group. There were few deaths during these periods, and no statistical analysis was conducted.

For patients with remitted/stable first-episode psychosis, compared with antipsychotic treatment maintenance, discontinuation over a period of at least 2–5 years resulted in higher relapse,

rehospitalization, and mortality rates and no differences in the discontinuation rates, psychiatric symptoms, and QOL. Therefore, maintaining treatment for at least 2 years is recommended for the average patient. Notably, 45.7% of patients who discontinued antipsychotic treatment after 12 months (76.0% for no discontinuation) and 39.4% of patients who discontinued antipsychotic treatment after 18–24 months (65.4% for no discontinuation) did not experience relapse. This is thought to have occurred because the target patients of this study included those not only with schizophrenia that required long-term antipsychotic treatment but also with diseases such as schizophreniform disorder and short-term psychotic disorder, in which symptoms disappear in a relatively short period of time. However, clinicians currently have no clinical tools or biomarkers to differentiate these patients. Therefore, clinicians should strive to make differential diagnoses of schizophrenia and other psychiatric disorders to the extent possible, and once a definitive diagnosis has been established, to consider the best course of treatment based on that diagnosis. Another question is how to deal with patients for whom a definitive diagnosis is difficult even after heeding the above advice? A clear answer to this question cannot be given in this guideline but considering that many patients relapse when antipsychotics are discontinued and that a large number of patients may be able to live a disease-free life without relapsing, SDM should be conducted regarding the treatment policy after the content of this CQ is made available to the patient and physician.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

None.

ETHICS STATEMENT

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