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Review Article

Appropriate Monitoring May Affect the Life Expectancy of Patients with Mental Disorders in Japan: Literature Review on Guidelines for Serious Physical Risks

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Summary

Although several guidelines have been proposed for the physical management of patients with mental disorders, there are many differences among these guidelines, and it is necessary to review the literature for clinical implementation in Japan. The purpose of this study was to conduct a literature review using PubMed and Web of Science to examine the following serious physical risks that may affect the prognosis of patients with mental disorders: 1) abnormal glucose and lipid metabolism, 2) electrocardiographic abnormalities, 3) lithium poisoning, 4) severe drug eruption, and 5) malignant syndrome. There were some similarities in the monitoring plans for abnormal glucose and lipid metabolism, electrocardiographic abnormalities, and lithium poisoning. It was therefore assumed that a plan suitable for the actual situation in Japan could be formulated from these similarities. For severe drug eruptions, it is highly useful to provide information on these side effects as part of psychological education in addition to complying with the description in the package insert. For malignant syndromes, we suggest that it is important to consider the direction of basic interventions such as discontinuation of antipsychotics, systemic monitoring and management, infusion of fluids, and additional treatments as necessary.

Key Words: Monitoring, life expectancy, Mental disorders, Psychotropic drug

Introduction

Although several guidelines have been proposed for the physical management of patients with mental disorders, there are many differences among these guidelines, and it is necessary to review the literature for clinical implementation in Japan. Psychotropic drugs used in the treatment of psychiatric disorders include those with a high risk of causing abnormalities in glycolipid metabolism and electrocardiography, as well as those with a narrow therapeutic range of blood levels that require careful management. Although several guidelines have been proposed for the physical management of patients with mental disorders, there are many differences among the guidelines, and a literature review is needed for clinical implementation in Japan. The purpose of this study is to conduct a literature review using an international database of clinical medical literature on the following serious physical risks that may affect the prognosis of patients with mental disorders: 1) abnormal glucose and lipid metabolism, 2) electrocardiographic abnormalities, 3) lithium poisoning, 4) severe drug eruptions, and 5) malig-

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nant syndromes.

Methods

The PubMed and Web of Science databases were searched for clinical medical literature. 1) For abnormalities of glucose and lipid metabolism, the search strategy in PubMed was (metabolic syndrome [TIAB] OR diabetes [TIAB] OR hyperglycemia [TIAB] OR dyslipidemia [TIAB] OR hypercholesterolemia [TIAB] OR hypertriglyceridemia [TIAB] OR hyperlipidemia [TIAB]) AND (Schizophrenia [TIAB] OR bipolar [TIAB] OR depression [TIAB] OR depressive [TIAB] OR epilepsy [TIAB] OR antipsychotic* [TIAB] OR antidepressant* [TIAB] OR anticonvulsant* [TIAB]) AND guideline* [TIAB]; 2) for ECG abnormalities, the search strategy was (Long QT Syndrome [TIAB] OR QT Prolongation [TIAB] OR torsade de pointes [TIAB]) AND (Schizophrenia [TIAB] OR bipolar [TIAB] OR depression [TIAB] OR depressive [TIAB] OR epilepsy [TIAB] OR antipsychotic* [TIAB] OR antidepressant* [TIAB] OR anticonvulsant* [TIAB]); 3) for lithium addiction the search strategy was Lithium [TIAB] AND (Schizophrenia [TIAB] OR bipolar [TIAB] OR depression [TIAB] OR depressive [TIAB] OR epilepsy [TIAB] OR antipsychotic* [TIAB] OR antidepressant* [TIAB] OR anticonvulsant* [TIAB]) AND guideline* [TIAB]; 4) for severe drug eruption, the search strategy was (Stevens-Johnson syndrome [TIAB] OR Toxic epidermal necrolysis [TIAB] OR Lyell's syndrome [TIAB] OR Hypersensitivity syndrome [TIAB] OR Drug reaction with eosinophilia and systemic symptoms [TIAB] OR symptoms [TIAB] OR Drug-induced hypersensitivity syndrome [TIAB]) AND (Schizophrenia [TIAB] OR bipolar [TIAB] OR depression [TIAB] OR depressive [TIAB] OR epilepsy [TIAB] OR antipsychotic* [TIAB] OR antidepressant* [TIAB] OR anticonvulsant* [TIAB]); and 5) for malignant syndrome, the search strategy was Neuroleptic Malignant Syndrome [TIAB] AND (Schizophrenia [TIAB] OR bipolar [TIAB] OR depression [TIAB] OR depressive [TIAB] OR epilepsy [TIAB] OR antipsychotic* [TIAB] OR The Web of Science search strategies were also constructed with the same contents as those in PubMed, and the databases were searched on the same day. Furthermore, a manual search was conducted to identify additional eligible studies. The references included for review were used as primary sources for the guidelines. For guidelines developed by the same entity, the most recent description of the relevant area was adopted. We excluded guidelines that did not primarily target patients with psychiatric disorders (schizophrenia, bipolar disorder, depression, and epilepsy), guidelines that were limited to populations with special backgrounds, original papers, letters, comments, and documents that were not available by the deadline, even if they targeted patients with psychiatric disorders. We excluded from inclusion those guidelines that were limited to populations with special backgrounds, original articles, letters and comments, and literature that was not available by the deadline, even if it was targeted to people with mental disorders.

Results

1) Abnormalities in glucose and lipid metabolism

Based on the method, we obtained 783 abstracts from PubMed and 1,010 from Web of Science, and 1,210 remained after excluding duplicates. After a manual search, we evaluated the results and found that 10 abstracts were consistent with the purpose of this report. Among Japanese guidelines, only the Guidelines for the Pharmacological Treatment of Schizophrenia[1] mention monitoring abnormalities in glucose and lipid metabolism in addition to referring to them as side effects of drugs, and as a supplement to the Clinical Questions (CQs), the guidelines provide an evaluation schedule that divides the frequency and monitoring items according to diabetes risk. In addition, when weight gain occurs, it is recommended to change medications from those with such high risk to those with low risk after discussing the risk of relapse/recurrence with the person concerned. However, there are no clear rules for dosage setting, rate of dose increase, or conditions for drug substitution. The American Psychiatric Association (APA) Guidelines for the Treatment of Schizophrenia[2] also mention weight gain and abnormal glucose metabolism as side effects and recommend changing to a lower-risk drug. Nonetheless, they do not clarify dosage setting, rate of dose increase, conditions for drug substitution, or monitoring schedule. The UK National Institute for Health and Clinical Excellence (NICE) guidelines on schizophrenia[3] state that guidelines on obesity, cardiovascular disease,

and type 2 diabetes should be consulted for rapid or excessive weight gain and abnormalities in glucose and lipid metabolism but do not specify specific measures for people taking psychotropic drugs. There is no explicit mention of measures specific to people taking psychotropic drugs, nor is there a clear monitoring schedule. The NICE guidelines on bipolar disorder[4] state that weight, body mass index (BMI), diet, nutrition, physical activity level, fasting glucose, HbA1c, and lipid profile should be checked at least once a year. The Maudsley Prescribing Guidelines[5] describe a monitoring schedule for weight, glycemia, and lipid profile[5]. Weight should be monitored frequently before the start of treatment, up to the third month, and then once a year, with measurement of abdominal circumference and BMI recommended if possible. Blood glucose should be monitored before the start of treatment, in the fourth to sixth months, and then once a year, with fasting recommended if possible. The lipid profile is presented for evaluation before the start of treatment, at 3 months, and then once a year. For both weight gain and abnormalities in glucose and lipid metabolism, if they occur, a change to a lower-risk drug is recommended, but the dosage regimen, rate of dose increase, and conditions for drug substitution are not clarified. The Canadian Network on Mood and Anxiety Disorders and the International Bipolar Disorder Society (CANMAT-ISBD) bipolar disorder guidelines[6] state that tests including fasting glucose and lipid profiles should be performed prior to initiating treatment and that periodic weight changes should be assessed in all patients. However, there is no mention of specific frequency, and it is stated that the risk of weight gain from the drug should be carefully considered. The British Association of Psychopharmacology (BAP) has also published guidelines for schizophrenia[7] and bipolar disorder[8] and has separate guidelines for the management of abnormalities in glucose and lipid metabolism under antipsychotic treatment[9], which includes detailed recommendations for monitoring. The guidelines state that these measurements should be taken before and at regular intervals after the start of treatment, and BMI should be assessed at least every 4 weeks for the first 12 weeks-ideally every week for the first 4 to 6 weeks and every 2 to 4 weeks for the next 12 weeks. They also recommend that weight should be assessed before, six months after, and one year after initiation and then assessed once a year. For the evaluation of blood glucose levels, the report acknowledges that HbA1c is useful for long-term evaluation of blood glucose control but says that fasting or as-needed blood glucose evaluation is appropriate in the early stages of psychotropic drug treatment and recommends that it should be performed after 12 weeks, six months, and then annually. Lipid profiles should also be assessed at 12 weeks, 6 months, and annually thereafter. The assessment should be repeated from the first step after any change in antipsychotic medication. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for schizophrenia[10] provide a monitoring schedule for BMI, waist circumference, fasting glucose, and fasting lipid profile that begins before dosing and continues through week 12, with relatively frequent assessments, and then eases to once per year. Again, a change to a lower-risk agent is recommended, but dosage setting, rate of dose escalation, and conditions for drug substitution are not clarified.

2) ECG abnormality

As a result of the search, we obtained 647 abstracts from PubMed and 1,449 abstracts from Web of Science, with 1,638 results excluding duplicates. The APA guidelines for the treatment of schizophrenia[2] recognize a QTc >500 msec as a threshold for concern but state that there is no absolute QTc value at which psychotropic medication should be discontinued. There is no absolute threshold for discontinuation of psychotropic drugs, although QTc >500 msec is recognized as a threshold of concern in the guidelines[2]. Factors that may increase drug blood levels (e.g., deficient metabolic activity, drug interactions, hepatic or renal disease), cardiac risk factors (e.g., congenital QT prolongation syndrome, structural or functional heart disease, bradycardia, family history of sudden cardiac death), and other risk factors (e.g., female sex, advanced age, history of drug-induced QT prolongation, acute disorders, fainting, low NICE guidelines on schizophrenia[3] or bipolar disorder[4] state that cardiovascular indicators should be checked regularly or at least annually. The Maudsley prescribing guideline[5] recommends an ECG monitoring schedule of once a year for patients with previous abnormalities or risk factors, in addition to

before initiation and on admission. The guidelines also state that all antipsychotics have the potential for sudden cardiac death but that QTc interval measurements should be considered within a week of reaching therapeutic doses, especially when using drugs that are considered to have a moderate to high risk of QTc prolongation. Moreover, they recommenda reduction in prescription medication or switching to a lower-risk medication when QTc is 440 to 500 msec in men or 470 to 500 msec in women and discontinuation of the suspected medication when QTc is >500 msec. The BAP guidelines for schizophrenia[7] call for a history of cardiovascular disease and family history of cardiovascular disease in all patients.[7] as well as attention to risk factors (increased BMI, smoking, diabetes, increased heart rate, blood pressure, cholesterol, liver disease, and low nutrition). Patients with multiple risk factors are also urged to avoid high doses and multiple medications. The WFSBP guidelines for schizophrenia[10] call for an ECG monitoring schedule prior to initiation and as often as once a year to prevent QT prolongation, including selection of low-risk drugs, assessment of cardiac risk factors, and avoidance of drug interactions.

3) Lithium poisoning

As a result of the search, 377 abstracts were obtained from PubMed and 648 from Web of Science, and the results excluding duplicates were 737, which were evaluated after adding those obtained by hand search, and 7 were found to be consistent with the main purpose of this report. The Japanese Society for the Study of Depression Treatment Guidelines I. Bipolar Disorder 201711) point out that the effective concentration and the concentration that causes addiction are close to each other for lithium and state that it should be measured approximately once a week at the beginning of administration or when the dose is increased and approximately once every two to three months during maintenance therapy. Moreover, the guidelines state that trough values (measured in the morning before taking medication) are preferable and that at least the measurement immediately after taking medication should not be used. The therapeutic concentration should be 0.4 to 1.0 mEq/L (mM), and when lithium therapy is discontinued, the dose should be reduced slowly over 2 weeks to 1 month to avoid increasing the risk of relapse.

The APA Bipolar Disorder Guidelines[12] recommend that lithium should be administered in divided doses, usually starting with a small dose, and titrating upward. Each time the dose is increased, the blood level should be checked. However, if a rapid dose increase is required or if toxicity is suspected, it is acceptable to check the blood level as soon as possible. The frequency of blood lithium monitoring is also recommended to be at least once every 6 months or more, even in calm patients. In addition, concomitant medications that should be avoided (diuretics, ACE inhibitors, NSAIDs, COX-2 inhibitors) and side effects of lithium should be mentioned in patient education. The NICE guidelines on bipolar disorder[4] recommend that renal function should be assessed every 2 to 3 months for the first 6 months of treatment, and thyroid function should be assessed once or twice during the same period, and then every 6 months or 1 year thereafter if the patient's condition remains stable. The NICE guidelines for bipolar disorder[4] state that blood lithium levels should be measured 1 week after initiation and then weekly after each dose change until steady state is achieved. However, it is recommended that blood levels be measured every 3 months for the first year of treatment and every 6 months thereafter. In the case of low adherence, if the most recent plasma lithium level is 0.8 mM or higher, measurements should occur every 3 months. In addition, evaluations of thyroid and renal function are recommended every 6 months, with more frequent testing in the presence of these dysfunctions or signs of elevated calcium. The Maudsley Prescribing Guidelines[5] recommend a starting dose of 400 mg (200 mg in elderly patients) and an evaluation of plasma levels after 7 days in addition to 7 days after each dose change. It is recommended that blood samples be taken 12 hours after the last dose, and thereafter, the plasma concentration should be checked every 6 months along with renal function, thyroid function, and calcium concentration. Furthermore, the guidelines state that the frequency of the test should be increased in patients taking drugs that interact with each other, elderly individuals, and those with chronic kidney disease. The CANMAT-ISBD bipolar disorder guidelines[6] recommend that blood lithium lev-

els should be assessed approximately 5 days after the most recent dose adjustment and that blood should be drawn 12 hours after the last dose. In the acute phase, two consecutive evaluations are recommended, and thereafter, evaluation every 3 to 6 months is indicated. The BAP guidelines for bipolar disorder[8] state that the starting dose of lithium should be 400 mg for patients with normal renal function, and lower doses should be used for elderly patients and those with renal dysfunction. To improve adherence, the authors suggest a single dose at night or twice a day if adverse effects on renal function are considered. Blood concentration monitoring should be performed after dose escalation, and blood samples should be taken 12 hours after the last dose. In the maintenance phase, the authors recommend evaluation of lithium levels every 3 to 6 months and renal and thyroid function every 12 months, even in patients whose condition has stabilized. The WFSBP bipolar disorder guidelines[13] recommend an evaluation of blood lithium levels every 3-6 months, and renal and thyroid function should be assessed according to risk, although there is no detailed description of dose increase in the acute phase. Beside the guidelines recommend evaluations of renal and thyroid function every 6-12 months, depending on the risk. In addition, although the rate of lithium dose increases or decrease is not specified, a decrease in plasma concentration of more than 0.2 mM is associated with risk of relapse. In addition, the guidelines indicate that patients should be educated about the symptoms of lithium poisoning and situations that increase the risk before lithium is administered.

4) Severe drug eruption

The search yielded 641 abstracts from PubMed and 1,294 abstracts from Web of Science, with 1,506 results excluding duplicates. After adding those obtained from the manual search to this list, we evaluated the results and found 7 sets of guidelines that were consistent with the main purpose of this report. Epilepsy Clinical Practice Guidelines 2018[14] list skin rash as a relatively common idiosyncratic reaction to drugs and Stevens-Johnson syndrome (SjS), drug-induced hypersensitivity syndrome (DIHS), and toxic epidermal necrolysis (TEN) as rare but serious reactions. If in doubt, patients should discontinue the suspected drug immediately and consult a dermatologist. In most cases, these side effects occur within 1 to 2 weeks to 2 to 3 months of starting the drug, so caution should be exercised in the early stages of treatment. The Japanese Society for the Study of Depression Treatment Guidelines I. Bipolar Disorder 2017[11] introduce SjS and Lyell syndrome as side effects of carbamazepine and lamotrigine. In particular, severe drug eruptions with lamotrigine are more frequently observed in patients whose starting dose was higher than the recommended dose and in patients who received lamotrigine in combination with valproic acid, and it is recommended to start with a small dose and titrate up slowly. The APA's Bipolar Disorder Guidelines[12] also mention SjS and TEN as side effects of carbamazepine and lamotrigine, and the section on carbamazepine states that these side effects occur within 3 to 6 months after initiation of treatment and early in treatment for lamotrigine. The carbamazepine section states that blood tests are unreliable in predicting the onset of these side effects and that it is essential to educate patients about the signs of severe drug eruptions. In the section on lamotrigine, the authors note that while dose escalation may reduce the incidence of severe drug eruption, concomitant use with valproate may increase the incidence. While it is difficult to distinguish between more severe and benign drug eruptions at the onset of severe drug eruptions, the committee expressed concern about those with fever and sore throat, diffuse and spreading to the face and mucosal tissues, and recommended discontinuation of lamotrigine (and valproate if used concomitantly) in such circumstances. The NICE guidelines on bipolar disorder[4] state that lamotrigine should be administered with caution to avoid interactions with valproic acid, to follow the instructions in the package insert, to consider gradual dose increases, and to contact a doctor immediately if a rash occurs during dose increases. The CANMAT - ISBD Bipolar Disorder Guidelines[6] state that patients starting carbamazepine or lamotrigine should be educated about the risk of rash, SjS and TEN and should be advised to contact their physician for appropriate treatment, including discontinuation of the suspected drug, if they develop rash or mucosal ulcers. In the BAP bipolar disorder[8] guidelines, the carbamazepine and lamotrigine sections mention severe drug eruptions such as SjS and TEN

as side effects. For the former, the dose is usually started at 400 mg and increased by 200 mg, and for the latter, the dose should be increased slowly. For carbamazepine, if fever, sore throat, rash, or oral ulcer occurs, the patient should seek medical attention as soon as possible, and for lamotrigine, it is difficult to determine whether the rash is serious or benign, but the suspected drug should be discontinued when it appears. The WFSBP guidelines for bipolar disorder[13] mention SjS as a side effect of carbamazepine and lamotrigine but do not provide details on dosage or decisions to discontinue the drugs.

5) Malignant syndrome

The literature search yielded 700 abstracts from PubMed and 902 from Web of Science related to malignant syndrome, and after excluding duplicates, we found 1,209 results, which were evaluated in addition to those obtained by hand search. The Japanese Guidelines for the Pharmacological Treatment of Schizophrenia[1] recommend discontinuation of antipsychotics, systemic monitoring and management, and physical therapy such as infusion of fluids when malignant syndrome occurs, as well as dantrolene, bromocriptine, and ECT as treatment options. The American Psychiatric Association's (APA) guidelines for the treatment of schizophrenia[2] state that symptoms typically occur within 72 hours after the use of dopamine antagonists and that the risk appears to be increased with higher potency first-generation antipsychotics. The guidelines also mention the possibility of increased risk with intramuscular injection, high doses, and rapid dose escalation. In most patients, improvement occurs within a week of stopping the antipsychotic. Treatment options in addition to discontinuation of antipsychotics include benzodiazepines such as lorazepam, dantrolene, bromocriptine, and ECT. The Maudsley-prescribing guidelines[5] list risk factors as high potency first-generation antipsychotics, recent dose increases, rapid dose increases, rapid dose reductions, abrupt discontinuation of anticholinergic medications, multiple medications, male sex, young age, and dehydration. If malignant syndromes occur, antipsychotics should be discontinued, and physical therapy such as systemic monitoring and management, infusions, benzodiazepines, dantrolene, bromocriptine, and electroconvulsive therapy (ECT) are listed as treatment options. It is recommended that antipsychotics be discontinued for at least 5 days (preferably more than 5 days) and restarted at very low doses. The BAP guidelines for schizophrenia[7] state that high doses of antipsychotics, rapid dose escalation, and use of high-potency drugs are risk factors and that the onset of malignant syndromes occurs early in exposure, within 24 hours in one in six cases, within one week in two-thirds of cases, and within 30 days in 96% of cases. Most patients will improve with recognition of symptoms and early discontinuation of the suspected drug, but if symptoms progress, additional measures such as fluid replacement and electrolyte correction may be required. High-potency benzodiazepines such as lorazepam, dantrolene, bromocriptine, and ECT are also recommended as treatment options, and the WFSBP Guidelines for Schizophrenia[10] recommend that antipsychotics be discontinued immediately in the event of a malignant syndrome, in addition to general measures. The WFSBP schizophrenia guidelines[10] list dantrolene and ECT as treatment options but state that they are not based on sufficient evidence. They recommend monitoring patients for at least two weeks after recovery from symptoms, avoiding risky approaches such as high doses and rapid dose increases, and titrating up from low doses of low potency or atypical antipsychotics.

Discussion

In this study, we conducted a literature review of guidelines in five areas: 1) abnormal glucose and lipid metabolism, 2) electrocardiographic abnormalities, 3) lithium poisoning, 4) severe drug eruptions, and 5) malignant syndromes. Although each set of guidelines recommends changing medications from high risk to low risk in all areas, the risk of worsening symptoms is also associated with this change, so a joint decision-making process such as consultation with patients may be useful.

Most of the guidelines on abnormalities in glucose and lipid metabolism have mainly been designed for the treatment of schizophrenia. Regarding monitoring, although there were some differences in details, the schedule was relatively frequent in the first 3 months of treatment and relaxed to once a year thereafter, except in high-risk patients.

For ECG abnormalities, most of them recommended testing approximately once a year, except for frequent testing before initiation and during dose increases. In addition to interviewing all patients about their history of cardiovascular disease and family history, it may be important to avoid high doses and multiple drug use in patients with multiple risk factors.

For lithium poisoning, most guidelines recommended testing approximately once every 6 months, except for frequent testing before starting and during dose increases. On the other hand, associated tests for thyroid function, renal function, and calcium levels were less frequent than those for measurement of lithium concentration, although the frequency varied among the guidelines.

Severe drug eruptions were rarely chaptered independently, and many guidelines listed them as side effects of carbamazepine or lamotrigine. For the latter, a common emphasis was often placed on slow dose escalation and caution with concomitant medications. Some of the guidelines reviewed herein required that patients be fully informed about the symptoms of severe drug eruptions and concomitant medications that may increase their risk. Since it may be difficult to indicate a monitoring plan for managing drug eruptions, it was considered highly useful to provide appropriate information on side effects as part of psychoeducation to enable early therapeutic intervention.

Regarding malignant syndrome, although there were differences in details, it appeared to be a side effect that could occur in the early stages of administration. The direction of discontinuation of antipsychotics and physical therapy, such as systemic monitoring and management and infusion, and additional treatments, such as benzodiazepines, dantrolene, bromocriptine, and ECT, were also common. However, there were some guidelines that stated that additional treatments were not based on sufficient evidence, and if symptoms improved with discontinuation of antipsychotics, systemic monitoring and management, and infusion, additional treatments may not be recommended for all patients.

Conclusion

A literature review was conducted on guidelines for serious physical risks that may affect the life prognosis of patients with mental disorders. There were some similarities in the monitoring plans for abnormal glucose and lipid metabolism, electrocardiographic abnormalities, and lithium poisoning, and it was inferred that a plan suitable for the actual situation in Japan could be developed from these. For severe drug eruptions, it is highly useful to provide information on these side effects as part of psychological education, in addition to complying with the description in the package insert. For malignant syndromes, we thought that we should consider the direction of basic interventions such as discontinuation of antipsychotics, systemic monitoring and management, infusion of fluids, and additional treatments as necessary.

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Author Contributions

NYF conceived and designed the study; NS acquired and analyzed the data; NYF drafted the manuscript; KS performed the final check of the content.

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