

JAPAN

By H. NAKAJIMA

Professor, 6-17 Sanbancho, Chiyoda-ku, Tokyo, Japan.

I. INTRODUCTION

Since 1970, the year of the First Seminar, there has not been any significant changes in psychotropic medication in Japan. The recent statistics indicate that the consumption of major and minor tranquilizers has not increased, except anti-depressants, especially amitriptyline which has been slightly increased because of the introduction of the term "masked depression". It is considered that this unique term has stimulated most probably the use of anti-depressants by non-psychiatric doctors.

According to the governmental statistics, the annual increase rate of the number of psychiatrists, psychiatric hospitals, and the beds for the psychiatric patients in psychiatric and general hospitals was stable, and the rate of schizophrenia and other psychosis followed the same tendency.

In Japan, psychotropic medication has become very popular and has taken the lead in the treatment of mental disorders.

Based on different statistics, it is estimated that a schizophrenia patient may annually consume important major tranquilizers worth about ¥90,000 (or US\$ 330) and that about 1 - 2 million of the Japanese take minor tranquilizers daily.

II. Actual Status of the Psychopharmacological Therapy for Psychiatric and Psychosomatic Diseases

A. Schizophrenia

1. Management of Schizophrenia Symptoms

The pharmacotherapy of schizophrenia is almost standardized in Japan. The different types of antipsychotic drugs will be selected mainly according to the symptomatology which may be classified into two different aspects, i.e. positive states such as hallucination, delusion and psychomotor excitation, and negative states mainly recognized by autistic symptoms.

a) Management of Excitation

Generally, the treatment is started by parenteral administration (i.m.) of Chlorpromazine or Levomepromazine (25 - 50 mg, 2 - 4 times per day) or Haloperidol (5 - 10

mg, i.m. or i.v.). Recently, it is confirmed that i.m. or i.v. administration of Diazepam (10 - 30 mg) obtained favourable results and are even more effective than dosage increase of antipsychotic drugs.

When tranquilization appears in patients, parenteral administration should be switched to oral administration of antipsychotic drugs, especially Haloperidol and Chlorpromazine.

b) Management of Stupor

Perphenazine and Fluphenazine are used most frequently in the following ways.

- Perphenazine is administered by starting with initial dosage of 6 - 12 mg/day and increasing up to 20 - 30 mg/day.
- Fluphenazine is effective with daily dosage of 3 - 6 mg/day.

Administration of Diazepam slowly and intravenously also releases patients from the state of stupor.

c) Hallucination and Delusion

The use of butyrophenone derivatives (Haloperidol) Trifluoperidol and Fluripamide) has recently become more familiar but Chlorpromazine is still more frequently used.

d) Diminution of Rapport and Reduction of Spontaneity

The phenothiazine which has the piperazine ring in side chain (Perphenazine 10 - 30 mg/day, Fluphenazine 1 - 5 mg/day) is most widely used. Carbipramine, which was originally developed in Japan, is indicated for this case and yields good results. However, the relapse in the acute phase may sometimes occur. These symptoms will most frequently appear in cases of chronic schizophrenia and are generally difficult to treat. However, several new antipsychotic drugs such as Clothiapine and Oxypertine claim special indication for these states.

e) Anxiety and Agitation

Anxiety state is frequently observed in schizophrenia, especially in its acute phase. In this case, the concomitant use of minor tranquilizers such as Diazepam and Medazepam with major tranquilizers such as phe-

nothiazine and butyrophenone is recommended.

2. Prevention of Relapse and Treatment for Remission.

The necessity of drug therapy during the period of remission to prevent the relapse is generally accepted. Generally speaking, the relapse may occur 3 – 6 months after reduction or ceasing of medication. The continuous medication and the occurrence of tardive side-effects, especially tardive dyskinesia has been recently discussed.

3. Drug Association and Interaction

The simultaneous use of two or more drugs with different pharmacological spectrums is frequently applied as a routine treatment of psychosis to obtain the potentiation of effects and/or to reduce side-effects. The use of Fluphenazine together with Levomepromazine is an example and the association of Chlorpromazine with Chlordiazepoxide may manage agitated patients better than Chlorpromazine alone. The confirmation of the interest of combination therapy has not been made yet while the problem on drug interaction has more and more attracted clinical doctors' attention. Therefore, we should pay more careful attention to the association of drugs in routine practice.

B. Treatment of Mania and Depression

In this field, two new topics are now discussed in Japan.

1. The treatment and the Possibility of Prevention of Manic Syndromes by Lithium Carbonate.

Even Lithium Carbonate has not yet received governmental approval as a new drug. Large-scale clinical trials have been performed all over the country. The following are the conclusions and problems.

- a) Lithium acts rather slowly and effects may be obtained within 4–10 days for those who respond to Lithium.
- b) The specific anti-manic effects of Lithium was discussed but some authors reported that Lithium was effective also for the manic state of symptomatic psychosis or schizophrenia.
- c) It is agreed that Lithium removes the manic state naturally, contrary to the major tranquilizers which suppress the symptoms and produce so-called "drug-produced state of quiet."

d) Blood (serum) concentration of Lithium ion and therapeutic effects.

The optimum therapeutic concentration will be located between 0.4 – 1.2 mEq/l according to the studies by Watanabe. The occurrence of toxic symptoms may be parallel with blood concentration of Lithium ion. The maximum safety level is around 1.5 mEq/l and toxic level more than 2.0 mEq/l.

e) The prevention of manic-depressive phase in cyclothymic psychosis by Lithium is now under investigation. However no conclusive evidence has been obtained. The long-range administration of Lithium should be done very carefully regarding the toxic side-effects.

2. Drug Therapy of So-called "Masked Depression"

Despite the hesitation of the psychiatrists, this new terminology is now widely used among the Japanese medical professionals. In almost all cases, the association of anti-depressants (mainly Amitriptyline) and minor tranquilizers (Diazepam and Medazepam) are applied to different kinds of psychotherapy including Morita therapy and hypnosis.

The choice and dosage of anti-depressants are the most important problems and the non-psychiatric practitioner prefers Amitriptyline to Imipramine. Due to possible adverse reactions of tricyclic anti-depressants, daily dosage of anti-depressants is determined as low as possible. In this respect, the combination of minor tranquilizers, especially benzodiazepine derivatives, seems to be useful. In certain cases, the administration of Medazepam alone has improved the depressive state.

For handling accompanying symptoms of depression, especially insomnia, the reasonable administration of hypnotics (Nitrazepam) is recommended.

In this connection, some practitioners who use the hypnotics as psychotherapy prefer Diazepam injection (i.v.) for the introduction of hypnosis.

C. Drug Therapy of Neurosis and Psychosomatic Diseases.

As mentioned in the introduction, it is estimated that 1–2 million of the Japanese (1–2% of population) consume minor tranquilizers of benzodiazepine derivatives per day. This means that each medical doctor (total: 113,214 in 1970) prescribes this kind of drugs for about 8 – 17 patients daily, and that if the case is limited to psychiatrists (total: 8,713 in 1970) about 100 – 200 patients are taken care by a psychiatrist

daily. As the latter seems too far from a fact, the drug treatment for neurosis and psychosomatic disease is handled not only by psychiatrists but all medical practitioners. Therefore, knowledge about psychotropic medication will be required more intensely by non-psychiatrists.

Two new benzodiazepine derivatives were introduced in Japan two years ago. One was Medazepam originated by Roche, and the other was Exazolam developed by Sankyo. According to the large-scale double blind trials of Medazepam against Diazepam, it was discovered that Medazepam was more effective on anxiety neurosis and phobia, and less effective on depressive neurosis. By symptoms, Medazepam was effective on anxiety and phobia and Diazepam on anxiety, depression and neurasthenia. In these double blind trials, the earlier onset of action of active drugs (Medazepam and Diazepam) was observed in comparison with placebo. The drugs were significantly more effective than placebo for 1 – 2 weeks after medication. Placebo group improved after 3 weeks of drug administration. Attention should be paid especially on the 2nd and 3rd week of medication, and doctors should at this period review again the efficacy and adverse reaction of drugs. The use of Meprobamate which was one of the most popular minor tranquillizers in the period of 1960's, was considerably reduced in Japan due to its adverse reactions.

III. Use of Psychotropic Drugs by Non-psychiatrists

As described in I. and II., the use of minor tranquillizers and anti-depressants spread among non-psychiatric practitioners in Japan. However, the use of major tranquillizers (antipsychotics) was mainly limited to psychiatrists. Generally speaking, psychiatrists were more interested in the efficacy of drugs and general practitioners were very anxious about the side-effects of drugs. When specialized drugs were used by non-specialized practitioners, the permanent safety of drugs should be assured.

Attention should be paid to psychotropic drugs which not only act on the specific function of the brain but might also modify the morphology, physiology and/or biochemistry of the whole body.

Most of the psychotropic drugs have an influence on the following systems and/or organs.

- a) Central Nervous System
 - (i) Sleep, awake
 - (ii) Paradoxical reaction

- (iii) Depressive reaction
- (iv) Manic state induced by anti-depressants
- (v) Manifestation of schizophrenic state
- (vi) Acute exogenous type reaction
- (vii) Paradoxical reaction
- (viii) Convulsion
- (ix) Others
- b) Extrapyramidal Syndrome
 - (i) Reversible: akinesia, Parkinsonism and acute dystonia
 - (ii) Irreversible: tardive dyskinesia
- c) Autonomic Nervous System
 - (i) Phenothiazine: Adrenolytic
 - (ii) Tricyclic anti-depressant: Anticholinergic
- d) Endocrine and Metabolic System
 - (i) Libido and potency
 - (ii) Menstruation disturbance
 - (iii) Lactation
 - (iv) Obesity and increase in body weight
 - (v) Diabetes mellitus
 - (vi) Liver and its appendages
 - (vii) Blood and hematopoietic organ
 - (viii) Skin and its appendages
 - (ix) Eye and other sensory organs
 - (a) Glaucoma
 - (b) Cornea and crystallina turbid
 - (c) Retina (pigmentary retinopathy)
 - (x) Cardiovascular organ
 - (a) Thrombosis, infarctus and phlebitis
 - (b) ECG
 - (xi) Effects on the foetus and reproduction system.

A careful and regular check of these systems organs is necessary when using psychotropic drugs in daily practice.

The effect of Major tranquillizers on extrapyramidal system and possible development of tardive dyskinesia becomes an important topic and antipsychotic drugs (Clozapine) which have no or few implications to extrapyramidal functions are now investigated.

The long-range administration of phenothiazine may act on the eye and may occasionally produce disturbance of the crystallina and cornea. Also, some phenothiazines cause retinitis pigmentosa.

The effects of tricyclic anti-depressants on the foetus and the cardiovascular system were also discussed.

The dependency liability and abuse of minor tranquillizers are continuously discussed. However, actual attentions are rather oriented to the relationship between the personality of the abuser

(host) and his social environment. This problem arises because amphetamine produces severe organic psychosis and abuse with very few physical dependency liability, while non-barbiturate hypnotics, methaqualon which produce endemic abuse in Japan has almost no dependency liability. There are only very few sporadic cases of marihuana abuse in Japan despite very frequent cultural exchange between U.S.A. and Japan.

The abuse of benzodiazepine derivatives has not been reported in Japan.

IV. Discussion on the Testing Principle for the General Assessment of Efficacy and Safety of Psychotropic Drugs

The following are recent topics of discussions on general problems of psychotropic medication.

1. Pharmacokinetics and metabolism.
2. Action of psychotropic drugs in normal subjects and in patients
3. Controlled trial for the evaluation of safety and efficacy
4. Studies on the dosage and duration of treatment.
5. Monitoring of the adverse reaction

The correlation between the efficacy and blood concentration of phenothiazines was studied by several authors. However, there is still no firm conclusion of the correlation. Tentative studies on the effect of anti-anxiety drugs (Diazepam and Bromazepam) in normal volunteers were performed by Ogawa et al. The results show that each drug acts differently on the subjects with higher anxiety level and on those with lower anxiety level.

The requirement for scientific evaluation of the efficacy and safety of drugs is now found in Japan. For the performance of this kind of trials, we are using Japanese originated rating scale because of the Japanese specific socio-cultural and language problems.

As mentioned in II. and III., the duration of administration of major tranquillizers is now under review in consideration of residual or long lasting effects after the long-range administration.

Since last year, Japan has been a member of the International Drug Monitoring System organized by the W.H.O. The methodology of intensive and passive monitoring for adverse reactions will

be a problem in the near future.

V. Conclusion

Psychotropic medications have been already well established in Japan and psychotropic drugs are now widely prescribed not only by psychiatrists but by all medical practitioners. According to this tendency, more careful attention not only to the efficacy of the drug but also to the safety of drugs will be stressed. Therefore, for the assessment of the safety and efficacy, several problems on testing principles were discussed.

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Table 1

1. Number of Doctors

	1969	1970
Neuropsychiatry	8,251	8,713
Internal Medicine	56,174	57,654

2. Number of Psychiatric Hospitals and Beds

	1969	1970	1971
Psychiatric Hosps.	874	896	900
" Beds	177,567	185,162	188,395
General Hosp.	—	—	—
" Beds	60,625	62,103	65,067

3. Number of Psychiatric Patients Actually Treated

	1969	1970	1971
Schizophrenia	160,000	151,000	165,000
Other Psychosis	2,500	2,500	2,700