Drug Therapy for Depression in Japan

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Abstract: Drug therapy for depression fails in more than half of the patients receiving it because inadequate doses are given. It must be explained before starting drug therapy that its effects only appear after 2–4 weeks, but side-effects develop immediately and then begin to subside after 1 week. As a rule, a single antidepressant is administered. SSRIs are as effective as tricyclic antidepressants, but their adverse effects are far weaker than those of the older drugs. This is an advantage of SSRIs over tricyclic antidepressants. According to the American version of the therapeutic algorithm for depression (1995), the first-line drugs for moderate depression are SSRIs. For servere depression, however, tricyclic antidepressants are more effective than SSRIs. To prevent the relapse of acute depression, drug therapy should be continued for 4–6 months at the same dose. When the patients have had two or more depressive episodes in the last 5 years, drug therapy must be continued without changing the dose for 2–3 years, or for 5 years if possible, to prevent recurrence.

Key words: Depression; Drug therapy; Evidence-based medicine (EBM); Selective serotonin reuptake inhibitor (SSRI)

Introduction

In recent years, drug therapy for depression has been undergoing the transition from experience-based medicine to evidence-based medicine (EBM) utilizing the findings of randomized controlled trials. To cope with the transition, the investigation of algorithms for EBM-oriented drug therapy is underway. Although it was far later than in many other countries, fluvoxamin was introduced as the first selective serotonin reuptake inhibitor (SSRI) for clinical use in Japan in 1999. Subsequently, another SSRI (paroxetin) and the first serotonin noradrenaline reuptake inhibitor (SNRI, milnacipran) have been successively released in Japan. Thus, all the types of new-generation antidepressants have now become clinically available in Japan, as in many other countries. These changes have propelled drug therapy for depression in Japan to a new level.

The prevalence of depression in the general population is 2–7%, with a lifetime prevalence of 4–19%, indicating that it is a very common

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Table 1 List of Antidepressants Clinically Available in Japan and Their Daily Doses

Nonproprietary name	Daily dose (mg)
Tricyclic antidepressants	
Imipramine	25–300
Amitriptyline	30–300
Trimipramine	50–300
Nortriptyline	20–150
Clomipramine	50–225
Amoxapine	25–300
Lofepramine	20–150
Dosulepin	75–150
Tetracyclic antidepressants	
Maprotiline	30–150
Mianserin	30–60
Setiptiline	3–6
Others	
Trazodone	75–200
Sulpiride	150–600
Selective serotonin reuptake inhibitors (SSRIs)	
Fluvoxamine	50–150
Paroxetine (2001～)	20–40
Serotonine noradrenaline reuptake inhibitors (SNRIs)	
Milnacipran (2001～)	50–100

disease. Among all patients, about one third seek attention at psychiatric clinics, with another one third being seen at other types of clinics. The remaining one third do not seek any medical assistance. Even at psychiatric clinics, depression is often overlooked. In addition, drug therapy fails to control depression in more than half of the patients receiving it because of inadequate doses. In the end, only one tenth of all patients with depression receive appropriate drug therapy.[1,2)]

This article provides an outline of drug therapy for depression following the introduction of the first SSRI in Japan, with the factors described above being taken into consideration.

Pharmacology of Antidepressants (Tables 1–3)

Antidepressants can be divided into two major classes: one is drugs that selectively inhibit the reuptake of monoamines such as serotonin and noradrenaline at the synapses and the other is tricyclic and tetracyclic antidepressants, which not only inhibit the reuptake of monoamines but also block various neurotransmitter receptors such as adrenergic α_1 and α_2, muscarinic (cholinergic), histamine H_1 and dopamine D_2 receptors. Antidepressants of the former class can be further divided into two subclasses, which are selective serotonin reuptake inhibitors that have a much stronger inhibitory effect on the reuptake of serotonin than that of noradrenaline (SSRIs) and drugs that inhibit the reuptake of both serotonin and noradrenaline (SNRIs).

Selective monoamine reuptake inhibitors have as strong an antidepressant action as tricyclic or tetracyclic antidepressants, but cause much less severe side-effects. This is an advantage over the older antidepressants, particularly during long-term treatment to prevent relapse or recur-

Table 2 *In vitro* Short-term Biochemical Activities of Selected Older and Newer Antidepressants. Adapted from Potter *et al.* (1991) and Pirmohamed *et al.* (1992), plus data from Richelson & Nelson (1984) and Lancaster & Gonzalez (1989a,b)

Drug	Reuptake inhibition			Receptor affinity				
	NA	5-HT	D	α_1	α_2	H_1	MUSC	D_2
Older drugs[a]								
Amitriptyline	±	##	0	###	±	###	###	0
Clomipramine	±	###	0	##	0	+	##	##
Desipramine	###	0	0	+	0	±	+	0
Dothiepin	±	±	0	±	0	###	###	0
Doxepin	##	+	0	###	0	###	##	0
Imipramine	+	+	0	##	0	+	##	0
Nortriptyline	##	±	0	##	0	+	##	0
Trimipramine	+	0	0	###	±	###	##	##
Newer drugs								
Amfebutamone (bupropion)	±	0	##	0	0	0	0	0
Amoxapine	##	0	0	##	0	+	0	##
Citalopram	0	###	0	0	0	0	0	0
Fluoxetine[b]	0	###	0	0	0	0	0	0
Fluvoxamine	0	###	0	0	0	0	0	0
Lofepramine	###	0	0	+	0		+	##
Maprotiline	##	0	0	##	0	###	+	+
Mianserin	0	0	0	###	##	###	0	0
Paroxetine[b]	0	###	0	0	0	0	±	0
Sertraline[b]	0	###	0	0	0	0	0	0
Trazodone	0	+	0	###	±	±	0	0

a: Tricyclic antidepressants.

b: Selective serotonin reuptake inhibitors.

Abbreviations and symbols: NA = noradrenaline (norepinephrine); 5-HT = 5-hydroxytryptamine (serotonin); D = dopamine; α_1 = α_1-adrenergic receptor; α_2 = α_2-adrenergic receptor; H_1 = H_1 histamine receptor; MUSC = muscarinic (cholinergic) receptor; D_2 = D_2 dopamine receptor; 0 = no effect; ± = equivocal effect; + = small effect; ## = moderate effect; ### = large effect; ### = maximal effect.

Source: Rudorfer, M.V. *et al.*: Comparative tolerability profiles of the newer versus older antidepressants. *Drug Saf* 1994; 10(1): 18–46.

rence, because poor compliance can be avoided. In addition, because of adverse effects on the central nervous system and cardiovascular system, these drugs are relatively safe even for elderly and/or debilitated patients. Unlike tricyclic antidepressants, these drugs are rarely lethal even when an overdose is taken for attempted suicide.

Fluvoxamine may cause side-effects such as gastrointestinal disorders (including nausea and decreased appetite), anxiety and irritation, tremor, impaired ejaculation, and the serotonin syndrome. Therefore, this drug should be used with careful consideration of such side-effects. The co-administration of drugs to potentiate gastric defensive factors may be effective in preventing the gastrointestinal side-effects of fluvoxamine, although the value of such combinations is largely unproven. Care must be taken when fluvoxamine is used because it is a potent inhibitor of cytochrome P-450(CYP)1A2 and thus blocks the metabolism of propranolol, theophylline, and warfarin. It also causes moderate inhibition of CYP3A4, and hence blocks the metabolism of antiallergic drugs (such as terfenadine or astemizole) and cisapride (a gastrointestinal prokinetic drug). Fluvoxamine should not be used in combination with any of

Table 3 Antidepressants Side-effects and Possible Clinical Consequences of Neurotransmitter Receptor Blockade by Antidepressants

Antihistamine H_1
Potentiation of central depressant drugs
Sedation, drowsiness
Weight gain
Hypotension
Antimuscarinic
Blurred vision
Dry mouth
Sinus tachycardia
Constipation
Urinary retention
Memory dysfunction
Anti-α_1-Adrenergic
Potentiation of the antihypertensive effect of prazosin (Minipress)
Postural hypotension, dizziness
Reflex tachycardia
Anti-α_2-Adrenergic
Blockade of the antihypertensive effects of clonidine (Catapress) and α-methyldopa (Aldomet)
Anti-dopaminergic
Antipsychotic effects
Extrapyramidal movement disorders: dystonia, parkinsonism, akathisia, tardive dyskinesia
Endocrine effects: increase of prolactin (galactorrhea, gynecomastia, and menstrual changes)

Source: Kanba, S. and Richelson, E.: Antidepressant interactions with neurotransmitter receptors *in vitro*; Prediction of potential side effects. Ed. O'Brien, R.A. In *Receptor Binding in Drug Research.* Mircel Dekker Inc., New York, Basel, 1986; pp. 429–477

these drugs because the inhibition of metabolism may result in QT prolongation and ventricular arrhythmia.

Acute Therapy

As a rule, acute therapy of depression is treated at outpatient clinics. When anxiety, irritation, or suicidal ideation is severe or the patient is unable to eat, hospitalization is necessary. Before starting drug therapy, it should be carefully explained to the patient and the family that: 1) depression is a brain disease that can be cured by drug therapy and rest, 2) the family should make allowance for the disease and should not encourage the patient to do too much, 3) drug therapy begins to have an effect after 2 to 4 weeks, and 4) side-effects develop immediately, but begin to subside gradually after about 1 week. In order to assess the effectiveness of drug therapy, a single antidepressant is usually administered. In the case of antidepressants, combined drug therapy has rarely evidenced an increase in efficacy.

When the treatment of moderate depression is tried from the perspective of EBM, there is no evidence that one antidepressant is superior to another in effectiveness. On the basis of antidepressant activity, consequently, drug therapy can be started with any antidepressant, but it is better for one having minimal side-effects be selected. According to the American version of the therapeutic algorithm (1995), the first-line drugs for initiating therapy are SSRIs.[3] Based on this policy, fluvoxamine and paroxetine become the drug of choice in Japan. According to the Japanese algorithm (1998) produced before the introduction of fluvoxamine, sulpiride and

the tricyclic or tetracyclic antidepressants are all regarded as first-line drugs.[4)]

Fluvoxamine is initially administered at a dose of 25–50 mg/day, which is increased to 75–100 mg/day after 1–2 weeks, if necessary. If the condition shows a tendency to improve after 2–3 weeks, treatment is continued without a further increase of the dose. If not, the dose can be increased to 150 mg. If the drug is ineffective despite administration at a higher dose for 4–6 weeks, fluvoxamine should be replaced with another antidepressant. If the alternative drug is one of the tricyclic antidepressants, the initial dose should be 75–100 mg/day. The dose is increased gradually once every two weeks if there is no response and an absence of side-effects or tolerable side-effects. It is desirable for the drug to be administered for 4–6 weeks or longer at an adequately high dose exceeding 150 mg or around 250 mg, if possible (see Table 1). Because antidepressants can lower the threshold for tremor at high doses, the patients should undergo electrocardiography and electroencephalography. When an antidepressant is given at such a high dose and fails to elicit any effect, it can be regarded as having failed and an alternative antidepressant should be used.

For severe depression, tricyclic antidepressants are more effective than SSRIs.[3)] Amitriptyline and clomipramine are the drugs of choice. Intravenous infusion of clomipramine and electroconvulsive therapy are used in some cases.

When depression is refractory to antidepressant monotherapy, the drugs are administered in combination with lithium, thyroid hormone, or bromocriptine (an antiparkinson agent) for potentiation of efficacy. The effectiveness of such combinations has been documented.[3,4)]

Remission is achieved with first-line drugs in 38% of patients. This rate increases to 61% and then 77% when therapy is continued by replacing the first-line drug with a second-line and then third-line drug, respectively. If fourth-line drugs and alternatives are given subsequently, remission is only achieved in another 9% in total. Depression resolves completely within 6 months after the start of drug therapy in 79% of all patients treated. During the subsequent 12 months, remission is only achieved in 2%.[5)] If depression is associated with psychotic features, the remission rate is even lower. For depression of this category, a combination of antidepressants and antipsychotic drugs is effective.

When depression is associated with insomnia, anxiety, and irritation, the combination of an antidepressant with a benzodiazepine is effective, particularly soon after the introduction of antidepressant therapy. When the response is inadequate, however, treatment should not be continued for more than 2–4 weeks. Generally, drug therapy is discontinued step-wise when the symptoms have been stabilized.[4)]

Continuation Therapy and Maintenance Therapy

1. Continuation therapy: To prevent relapse before the termination of a depressive episode

Drug therapy for a first episode is continued for 4–6 months without changing the dose. For second and subsequent episodes of depression, treatment is continued the same period as for the previous episode.[6-9)]

2. Maintenance therapy: Prevention of recurrence and new depressive episodes

After a first depressive episode, depression will recur within one, five, and ten years in 28%, 68%, and 75% of patients, respectively.[10)] Among patients receiving long-term drug therapy with fluvoxamine at an average dose of 100 mg/day for 2 years, the recurrence rate was 20%.[11)] The rate for patients receiving imipramine at a dose of 200 mg/day for three and five years was 21%[12)] and 9%,[13)] respectively. If a patient has had two or more depressive episodes in the previous five years, it is desirable for prophylactic therapy to be continued for 2–3 years at the same dose as that used during

acute treatment and for 5 years, if possible.[11,13)]

Conclusion

Drug therapy for depression fails to work in more than half of the patients receiving it. In particular, tricyclic antidepressants are very likely to cause adverse events, and have failed to elicit a sufficient clinical response in patients receiving these drugs at inadequate doses because of such adverse effects. This has been partly responsible for the frequent occurrence of therapeutic failure. Because two SSRI drugs (fluvoxamin and paroxetine) and an SNRI (milnacipran) have now become clinically available in Japan, more patients with depression can receive adequate doses of antidepressants at present. With the advent of this new stage in the treatment of depression, it is hoped that psychiatrists will not overlook depression and depressive states that can easily be improved by drug therapy, even if the response is not perfect. In other words, it is important to identify patients with the indications for aggressive drug therapy as completely as possible.

REFERENCES

1) Shapiro, S., Skinner, E.A., Kessler, L.G. *et al.*: Utilization of health and mental health services. Three epidemiologic catchment area sites. *Archi Gen Psychiatry* 1984; 41 (10): 971–978.
2) Katon, W., von Korff, M., Lin, E. *et al.*: Adequacy and duration of antidepressant treatment in primary care. *Med Care* 1992; 30 (1): 67–76.
3) Nelson, J.C., Docherty, J.P., Henschen, G.M. *et al.*: Algorithms for the treatment of subtypes of unipolar major depression. *Psychopharmacol Bull* 1995; 31 (3): 475–482.
4) Shioe, K., Kubota, M., Shinohara, M. *et al.*: Therapeutic algorithms for major depression. Edited by Sato, K., Higuchi, T. and Yamawaki, N.: *Therapeutic Procedures for Schizophrenia and Mood Disorders*. Seiwa Shoten, Tokyo, 1998; pp. 63–74. (in Japanese)
5) Naganuma, H.: Outcomes of drug therapy for acute phase mood disorders. *No to Seishin no Igaku (Brain and Mind Medicine)* 1999; 10: 1–8. (in Japanese)
6) Frank, E., Kupfer, D.J., Perel, J.M., Cornes, C. *et al.*: Comparison of full-dose versus half-dose pharmacotherapy in the maintenance treatment of recurrent depression. *J Affect Disord* 1993; 27 (3): 139–145.
7) Furukawa, J.: Drug therapy for major depression. Edited by Otsuka, T., Kazamatsuri, H., Kitamura, T. *et al.*: *Evidence-Based Psychiatric Therapy*, Nippon Hyoron Sha, Tokyo, 1998; pp. 17–29. (in Japanese)
8) American Psychiatric Association: Practice guideline for major depressive disorder in adults. *Am J Psychiatry* 1993; 150 (4 Suppl): 1–26.
9) Task Force of the Collegium Internationale Neuro-Psychopharmacologicum (CINP): Impact of neuropharmacology in the 1990 — Strategies for the therapy of depressive illness. *Eur Neuropsychopharmacol* 1993; 3 (2): 153–156.
10) Lavori, P.W., Keller, M.B., Scheftner, W.A. *et al.*: Recurrence after recovery in unipolar MDD: An observation follow-up study of clinical predictors in somatic treatment as a mediating factor. *Int J Methods in Psychiatr Res* 1994; 4: 211–229.
11) Franchini, L., Gasperini, M., Perez, J. *et al.*: A double-blind study of long-term treatment with sertraline or fluvoxamine for prevention of highly recurrent unipolar depression. *J Clin Psychiatry* 1997; 58 (3): 104–107.
12) Frank, E., Kupfer, D.J., Perel, J.M. *et al.*: Three-year outcomes for maintenance therapies in recurrent depression. *Arch Gen Psychiatry* 1990; 47 (12): 1093–1099.
13) Kupfer, D.J., Frank, E., Perel, J.M. *et al.*: Five-year outcome for maintenance therapies in recurrent depression. *Arch Gen Psychiatry* 1992; 49 (10): 769–773.