Characteristics and Use of New Antidepressant Drugs

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Abstract: Japan has been considered at least ten years behind international standards in its use of antidepressant drugs, because selective serotonin reuptake inhibitors (SSRIs), which are mainstream antidepressants in Europe and North America, were not introduced in Japan until recently, and conventional tricyclic antidepressants had to be used instead. The first SSRI became available in Japan in 1999, followed by a newer type of antidepressant, i.e., serotonin-noradrenaline reuptake inhibitors (SNRIs), leading to more advanced treatment of depression. SSRIs are similar to conventional tricyclic antidepressants in their rate and onset of efficacy. However, since they act only on serotonin, they are associated with fewer side effects, and thus are easier for both patients and physicians to use. SNRIs potentiate the action of norepinephrine in addition to that of serotonin, and, theoretically, are expected to be more potent than SSRIs. However, their characteristics are similar to those of SSRIs. These new antidepressants are expected to be effective for anxiety disorders as well as depression, and may be useful in helping reduce the overprescription of benzodiazepine derivatives in Japan.

Key words: Antidepressant; SSRI; SNRI; Depression

Introduction

Japan has been considered to be at least ten years behind international standards in its use of antidepressants, because selective serotonin reuptake inhibitors (SSRIs), the mainstream antidepressants used in Europe, North America, and elsewhere, were introduced late in Japan, forcing Japanese physicians to depend on tricyclic antidepressants, an older generation of drugs for the treatment of depression.

However, in 1999, the first SSRI, fluvoxamine, was introduced in Japan, and another SSRI, paroxetine, became available the following year. Subsequently, milnacipran, a serotonin-noradrenaline reuptake inhibitor (SNRI), one of the newer antidepressant drugs, also became available, creating rapid changes and new devel-
Properties and Problems of Conventional Tricyclic Antidepressants

It is important to look initially at the properties and problems of antidepressant drugs of the previous generation.

Tricyclic antidepressants were first developed about 40 years ago. As mentioned above, they were the main antidepressants administered clinically in Japan until recently. Imipramine, a representative tricyclic antidepressant, was gradually improved, to produce a number of other newer tricyclic antidepressants. The basic properties of the newer derivatives are similar to those of imipramine; they inhibit the reuptake of serotonin and noradrenaline in nerve cells in the brain, thereby enhancing neural transmission and exerting an antidepressant effect.

The results of previous clinical trails indicate that the efficacy rate of tricyclic antidepressants in patients with depression is about 70%, a reasonably good rate. On the whole, tricyclic antidepressants can be regarded as effective drugs. However, the fact remains that about 30% of patients do not respond adequately to these drugs, and efforts to increase efficacy are important. In addition, tricyclic antidepressants require 3–4 weeks of uninterrupted therapy at adequate doses before their effects manifest. In other words, they are not fast-acting. Because depression is distressing to the patient and carries a high risk of suicide, the slow action of drugs in this class is a detriment to their efficacy.

However, a greater problem in the use of tricyclic antidepressants is their substantial side effects, the greatest drawback of drugs in this class. All tricyclic antidepressants block central and peripheral muscarinic receptors, histamine receptors, and α1 adrenergic receptors. Blockage of these receptors causes side effects including thirst, constipation, drowsiness, and dizziness on standing, leading patients to regard them as problematic and to take a negative attitude toward treatment. In addition, the tricyclic antidepressants induce an increase in ocular tension, making them difficult to use in patients with narrow-angle glaucoma. They may also worsen difficulty in urination in patients with benign prostatic hyperplasia, so that caution regarding their use is necessary in such patients. Thus, they can be difficult to use in the face of concomitant physical disease.

Because of these drawbacks, tricyclic antidepressants failed to gain the unmitigated trust of patients and physicians alike, despite their fairly high rate of efficacy. The attempt to overcome these drawbacks provided the impetus for the development of new antidepressant drugs.

Properties and Use of SSRIs

Among the new antidepressants, SSRIs will be discussed first. Five of the drugs in this category are used throughout the world, and two of them, fluvoxamine (Luvox®, Depromel®) and paroxetine (Paxil®), are available in Japan.

SSRIs are characterized by their relatively uncomplicated chemical properties. As mentioned previously, conventional tricyclic antidepressants not only have a potent inhibitory action on the reuptake of noradrenaline and serotonin in brain cells but also have blocking actions on various receptors in the body, resulting in substantial side effects.

However, SSRIs have hardly any such blocking effects, and their chemical action serves to inhibit serotonin reuptake alone. Thus, their side effects are minimal, while their rate of efficacy is similar to that of the tricyclic antidepressants. Thus, SSRIs are considered to have none of the undesirable effects of the tricyclic antidepressants, while managing to retain their useful properties.

Although some consider an efficacy rate similar to that of the tricyclic antidepressants
insufficient, the lack of problematic side effects has led to better patient compliance; consequently, better therapeutic efficacy can be expected from these drugs. In addition, if taken in large quantities for the purpose of committing suicide, the SSRIs are relatively safe because their lethal doses are much higher than those of the tricyclic antidepressants, another definite advantage of this class of drugs.

Although they represent a great step forward, the SSRIs are not without drawbacks. Apart from side effects, they retain the main deficiencies of the tricyclic antidepressants: they are not fast-acting; their efficacy rate remains at about 70%; and there is no incremental benefit in intractable cases, an effect naturally anticipated from novel drugs. Some reports have even documented that conventional tricyclic antidepressants are superior to SSRIs in severe cases.

In addition, it is not true that SSRIs have no side effects. About 10% of patients experience rather severe gastrointestinal symptoms such as nausea in the early phase of therapy. Another reported defect of SSRIs is their interactions with other drugs. This is because SSRIs inhibit cytochrome P450, the drug-metabolizing enzyme in the liver, causing blood concentrations of other drugs metabolized by this enzyme to increase.

As an example, caution is necessary when SSRIs are used in combination with antiasthma drugs, other antidepressants, or hypnotics. Common drugs that should not be combined with SSRIs include the antiasthmatic theophylline, the gastrointestinal motility-enhancing drug cisapride, and the antiallergic drug terfenadine. For detailed information on drug interactions, readers are referred to the package inserts and other material on SSRIs.

In summary, while it is true that SSRIs have fewer side effects and are clearly easier to use than conventional tricyclic antidepressants, because of the chance of nausea in the early phase of therapy, it is prudent to begin with a low dose and to increase the dose weekly to a sufficient dose. After that the same drug should be used continuously for at least 3–4 weeks to examine the patient’s response. If therapy is not effective, switching to a tricyclic antidepressant or a serotonin-noradrenaline reuptake inhibitor (SNRI) should be considered. Caution should be exercised if other drugs are being used concomitantly.

Properties and Use of SNRIs

The most recently developed antidepressants are the serotonin-noradrenaline reuptake inhibitors (SNRIs). In Japan, milnacipran (Toledomin®) has been used for two years, and currently it is the only SNRI antidepressant available.

As mentioned previously, SSRIs may be less effective for severe cases than tricyclic antidepressants because SSRIs inhibit the reuptake of serotonin alone and do not activate noradrenaline. Enhancing the function of a single neurotransmitter is not sufficient to diminish depression.

In this regard, drugs that activate both serotonin and noradrenaline, like the tricyclic antidepressants, do not have unfavorable effects such as blockade of muscarinic receptors and histamine receptors, and may be ideal in terms of potent clinical effects and minimal side effects. SNRIs were developed on the basis of this hypothesis. Thus, SNRIs are not just empirical drugs, but drugs that have been developed on the basis of a theory.

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Some studies have found SNRIs superior to SSRIs in clinical efficacy, and meta-analytical data has demonstrated this superiority. These data indicate that the aim of SNRI development has been achieved. However, most Japanese clinicians are under the impression that tricyclic antidepressants, SSRIs, and SNRIs are almost equal in efficacy, rather than considering SNRIs superior to SSRIs or tricyclic antidepressants. Nevertheless, SNRIs are reassuring because they do not carry the risk of interaction with other drugs, unlike SSRIs. This may well be considered the greatest advantage of SNRIs.

SNRIs have only a short history of use in Japan and elsewhere, and their true value, including optimal administration, remains to be established. To summarize the standard usage of milnacipran, therapy should begin with a low daily dose of 50 mg, which should be increased to 100 mg in 1 week unless there are particular adverse reactions, with maintenance at the same level for about 3 weeks. Although the package insert for this drug specifies 100 mg as the upper limit, some physicians suggest that a dose of 150 mg is more effective in actual clinical use. Since SNRIs have almost no interactions with other drugs, it seems easier to use SNRIs than SSRIs in combination with tricyclic antidepressants when the patient has not responded favorably to the maximum dose regimen. However, sufficient data on the efficacy of this combination have yet to be obtained.

### Expansion of Indications for SSRI and SNRI Therapy

Finally, increasing indications for treatment with these new antidepressant drugs will be discussed briefly. Antidepressant drugs are, of course, mainly indicated for depression. However, it has been indicated that both SSRIs and SNRIs are effective for anxiety disorders. Thus, the indications of their use are expanding. The use of fluvoxamine, an SSRI antidepressant, for obsessive-compulsive disorder, and the use of paroxetine, another SSRI, for panic disorder are currently covered by the national health insurance in Japan. The efficacy of SSRIs for post-traumatic stress disorder (PTSD) and anthropophobia has been suggested by a number of papers published in

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### Table 1: Comparison of New and Conventional Antidepressant Drugs

<table>
<thead>
<tr>
<th>Effiency rate</th>
<th>Tricyclic antidepressants</th>
<th>SSRIs</th>
<th>SNRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast-acting property</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Anticholinergic side effects</td>
<td>Strong</td>
<td>Almost none</td>
<td>Almost none</td>
</tr>
<tr>
<td>Adverse effects on digestive system such as nausea</td>
<td>Almost none</td>
<td>Rather marked</td>
<td>Slight</td>
</tr>
<tr>
<td>Interaction with other drugs</td>
<td>Almost insignificant</td>
<td>Significant in some cases</td>
<td>Not significant</td>
</tr>
<tr>
<td>Effects on diseases other than depression</td>
<td>Some are effective for panic disorder and obsessive-compulsive disorder.</td>
<td>There is corroborative evidence of efficacy for panic disorder and obsessive-compulsive disorder.</td>
<td>Efficacy for some anxiety disorders has been suggested.</td>
</tr>
</tbody>
</table>
Europe and North America. In these regions, the efficacy of SNRIs for generalized anxiety disorder has also been emphasized.

These anxiety disorders have commonly been treated with antianxiety drugs such as benzodiazepine derivatives. However, it is likely that SSRIs and SNRIs will become the main therapeutic choice in these cases. If so, the problem of psychological dependence on benzodiazepine derivatives may be greatly reduced. Hope is being placed on the new antidepressants in this regard. Table 1 summarizes the properties of tricyclic, SSRI, and SNRI antidepressants.

REFERENCES