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**Original Research**

# Development of antipsychotics in Japan

Masatoshi TAKEDA *President, Aino University*
Yukie MIZOGUCHI *Associate Professor Tenri Health Care University*

**Abstract**

The era of pharmacotherapy in Japan was opened with chlorpromazine developed in 1955. Since then Japanese Pharmas were quite energetic in developing new antipsychotics with little modification. Availability of so many antipsychotics may have led Japanese psychiatric service too much relied on antipsychotics. The era of the second generation antipsychotics (SGA) in Japan began with introduction of risperidone in 1996. Since then Japanese Pharmas produced SGAs such as perospirone, blonanserin, and aripiprzol, some of which have attained a great success in the world.
More and more SGAs will be introduced to Japanese market including brexpirazol, and lurasidone. Japanese psychiatrists are expected to be experts in utilizing these new SGAs, but it should be kept in mind of all psychiatrists that psychiatric service can be attained through the good practice in cooperation with the patients and their families and the role of antipsychotics should be re-evaluated considering the right direction in developing better clinical service to psychiatric patients.

**Key words**: antipsychotics, first generation antipsychotics (FGA), second generation antipsychotics (SGA), serotomin-dopamine antagonist (SDA), Japanese Pharma

## 1. Introduction

The psychiatric treatment and care of schizophrenia in Japan has significantly changed since the 1950s. One of the promoting factors for this change was the introduction of antipsychotics use. After chlorpromazine, new antipsychotics have been developed one after another by Japanese pharmaceutical companies, and we, psychiatrists in Japan, have been trained to be experts of utilizing these antipsychotics for the betterment of schizophrenia patients.

Looking back the history of psychiatric service in Japan in the latter half the previous century, the author claims that some part of our expereince in psychiatric service was not always heading for the right direction. Japanese psychiatrists were keen in utilizing and manipulating many antipsychotics, simply believing these drugs should bring better effects to schizophrenia patients. We might be too much influenced by the imaginary effects of newly developed antipsychotics. All the means we relied on were not the best choice for the patients, and the author believes that we could have done in different ways counting on more on psychotherapy and other psychiatric management methods in addition to pharmacotherapy.

As shown in Figure 1, the number of psychiatric hospitals sharply decreased in the United States since the 1960s, but the number of psychiatric hospitals rapidly increased in Japan. In Italy, closing of psychiatric hospitals was recommended as the national policy, and the number of psychiatric beds decreased linearly after 1975. During this time, however, the number of psychiatric beds still increased in Japan, reaching the maximum psychiatric beds of 360 thousands in 1996 (Fig. 1).

Since the 1970s, the psychiatric service has been drastically shifted from "the hospital based treatment" to "the community-based treatment" in the world. Japanese psychiatry seems to have been too late to catch up to this new paradime shift. It was only in the 2000s when the decrease in the number of psychitric beds was observed in Japan. Too much genuine expectation to antipsychotics use might have affected this delay in shifting from the hospital-based treatment to the community-based management of schizophrenia patients in Japan.

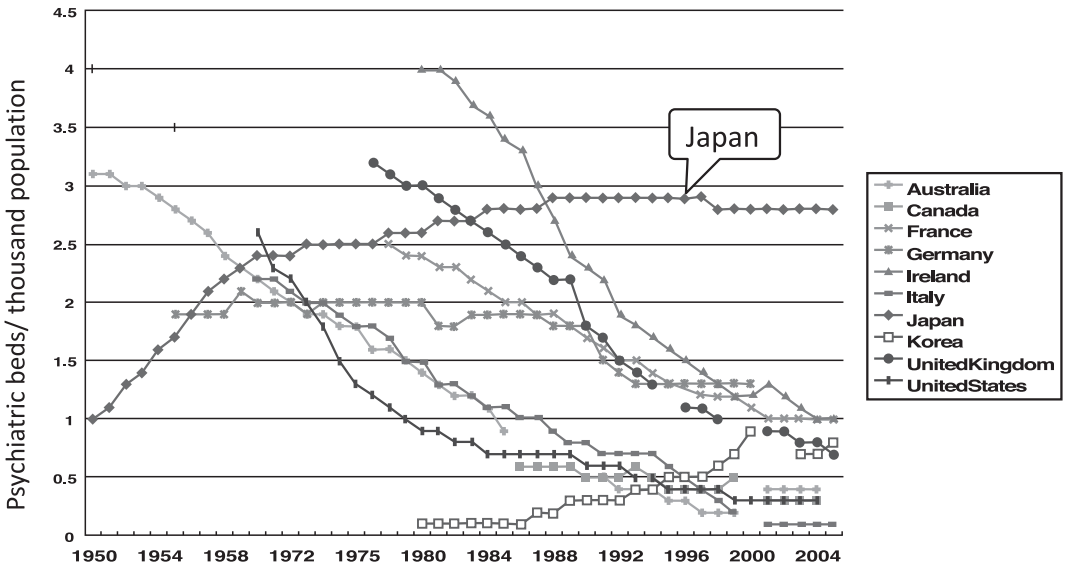


Figure 1 Change in psychiatric beds in OECD countries

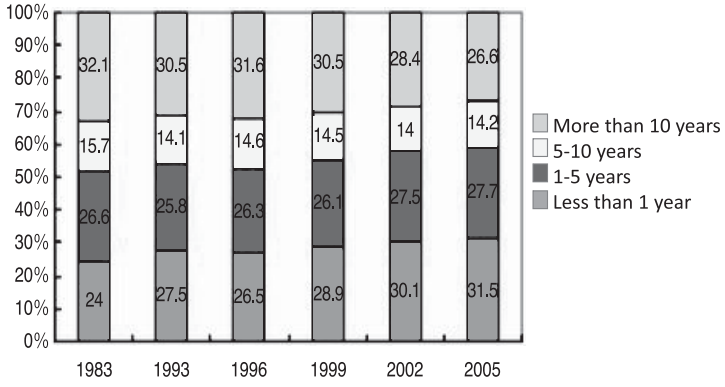


Figure 2 Length of stay in psychiatric hospitals in Japan

Even though the average hospital-stay of psychiatric patients in Japan has been gradually decreased from 530 days in 1980 to 300 days in 2008, it is still significantly longer than those in other countries which is less 50 days. Figure 2 demonstrates that 26.6% of psychiatric beds are occupied by inpatients staying more than 10 years and 14.2% are by the inpatients for 5–10 years, implying that 40% of psychiatric beds in Japan are still used for those chronic patients who should better be cared under the policy of the community-based management.

In this article, the author would like to describe the future direction of psychiatric treatment in Japan, after looking back on the history of the development of antipsychotics in recent 50 years in Japan.

## 2. Brief description of antipsychotics

An overactivity of the dopamine pathways is presumed to be the pathogenetic process of schizophrenia, and dopamine receptor antagonists are used to treat the symptoms of schizophrenia. Many antipsychotics were developed as therapeutic agents against schizophrenia since 1952, sometimes called "neuroleptics" because of its antagonistic action to monoamine receptors including dopamine receptor.

Several dopamine receptor subtypes are identified. D1 receptor family, stimulating cAMP, includes D1 and D5. D1 is located in striatal, limbic and cortical pathways ; D5 in striatal and limbic pathways. On the other hand, D2 receptor family, inhibiting cAMP, is located in wider cortical areas ; D2 in striatal, limbic and cortical pathways, D3 in limbic and cerebellar pathways, and D4 in limbic and cortical pathways.

The pharmacological action of antipsychotics is originally targetted to the blocking of dopamine D2 receptor. Though different antipsychotics have a different potency of D2 blockade, compari-

son of antipsychotic drugs shows that D2 receptor blocking action correlates well with the clinical dose, implying the D2 blockade action is explaining clinical effects to schizophrenia patients in contrst to non-relationship with D1 blocking action (Fig. 3).

Dopamine D2 receptor occupancy of 65–80% is regarded to be the optimal dose of the drug. Antipsychotics need to occupy D2 receptor more than 65% to have the clinical effectiveness. When D2 receptor occupancy exceed 80%, adverse side effects including extrapyramidal symptoms (EPS) occur and the clinical benefits of antipsychotics do not increse above 80% of D2 receptor occupancy (Fig. 4).

Two prototypes of antipsychotics are chlorpromazine developed in 1952, and haloperidol developed in 1957. Chlorpromazine is a highly effectinve D1 and D2 blocker, with blocking activity of some 5HT, ACh, histamine and $\alpha$ adrenergic receptors. This means that it can often cause pronounced sedation, moderate antimuscarinice effects and moderate extrapyramidal side effects. Haloperidol is more selective for DA receptors so has a better side effect profile, although EPSs are still a concern. It can also cause a rise in prolactin levels.

Numerous antipsychotics have been developed, trying to increase the clinical utility aiming for either more sedative action or anti-psychotic action. When antipsychotics are plotted in the two-dimensional map with anti-psychotic action (X axis) and sedative action (Y axis), the characteristics of these antipsychotics are easily understood (Fig. 5).

It was difficult to attain the goal of developing ideal antipsychotics under the hypothesis of D2 blocking action. In 1984, Paul Janssen developed a new type of antipsychotics, risperidone, which has atypical feature of receptor binding activity. Risperidone has more antagonist action to 5-HT2 and less antagonist action to D2, and alpha 1 & 2 receptors, with little or no binding to histamine, D1 and 5-HT1 receptors. Risperidone was de-

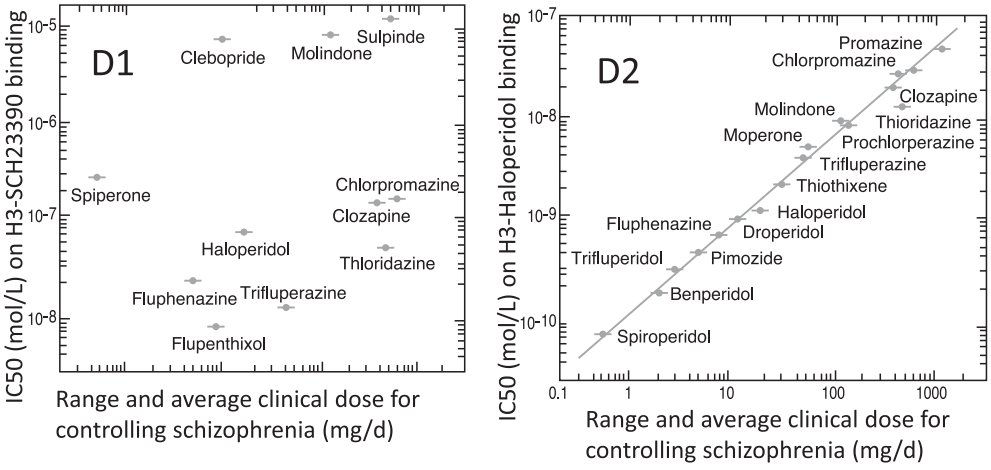


Figure 3 Correlation between clinical dose of various antipsychotics and D1, D2 blocking activity

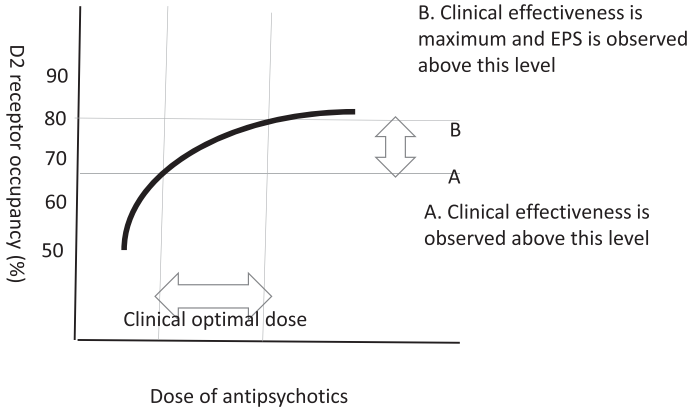


Figure 4 Clinical dose of antipsychotics and D2 receptor occupancy

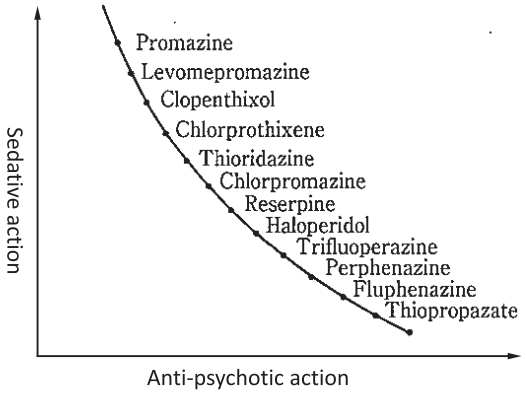


Figure 5 Anti-psychotic and sedative action of antipsychotic drugs (Kielholz P, 1969)

monstrated to have high clinical effectiveness with significantly less EPS and prolactin side effects than previous antipsychotics. Risperidone is termed as "atypical antipsychotics" because its effectiveness is quite different from the previous antipsychotics with D2 blocking action which are called "typical antipsychotics". After the success of risperidone, several atypical antipsychotics have been developed including quetiapine, clozapine, and olanzapine. Clozapine has more D1 and D4 blockade action, than D2 blockade, implying little EPS risk. Clozapine has anticholinergic and antimuscarinic side-effect and a risk of agranulocytosis. Olanzapine has antagonistic action to 5-HT2A, H1, and M1 receptors and less antagonistic activity to 5-HT2C, D2, $\alpha$1, and D1 with low risk of EPSs or prolactin side effect. Olanzapine's side effects include sedation, weight gain, dizziness, dry mouth, constipation and possible glucose dysregulation. Quetiapine shows antagonistic action to H1, 5-HT2, $\alpha$2, D2 in this order and the side effects profile is the same with those of olanzapine. These drugs have different pharmacological profile and different side effect.

## 3. Antipsychotics Use and Psychiaric Service in Japan

In Japan, the era of pharmacotherapy to schizphprenia began soon after the development of chlorpromazine in Europe. Yoshitomi Pharma obtained the patent for chlorpromazine synthesis of its own methods, and launched Contomin® as the first antipsychotics in 1955.

Figure 6 shows the four stages in the history of pharmacothery in Japan; days of monotheray (1955–1960), days of add-on therpy (1960s and 1970s), days of polypharmacy therapy (1990s) and days of the second generation antipsychotics (after 2000).

The introduction of antipsychotics had a major impact on treatment of schizophrenia, and contributed to the opening of new care for schizophrenia patients in psychiatric hospitals. Chlorpromazine and levomepromazine were used to calm down the excitement state of schizophrenia patients and to maintain patients' long stay in psychiatric hospitals. Antipsychotics had become almost essential tool in psychiatric service, and many antipsychotics of phenothiazine derivatives,

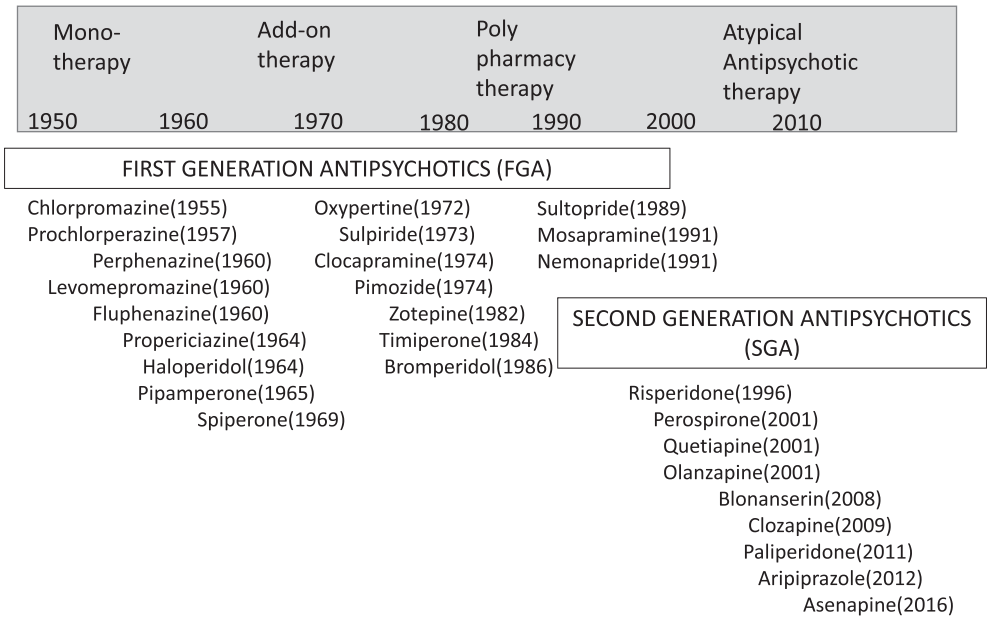


Figure 6 Four stages of pharmacotherapy in Japan

prototyped with chlorpromazine, were developed by Japanese pharmaceutical companies such as Yoshitomi Pharmaceutical, Fujisawa Pharmaceutical, Shionogi Pharmaceutical, and others. Psychiatrists were challenged by the task of choosing the best antipsychotics among many phenothiazine antipsychotics because antipsychotics had many adverse side effects such as extrapyramidal symptoms (EPS), constipation, orthostatic hypotension, dizziness, sleepiness, and others. To minimize those adverse side effects of antipsychotics, anticholinergic drugs were often prescribed in combination with phenothiazine antipsychotics.

In 1964, butyrophenone antipsychotics, haloperidol, was introduced in Japan, whose anti −hallucination/ delusion effects were soon recognized by Japanese psychiatrists, and haloperidol became the first choice drug to schizophrenia patients. The reputation of haloperidol, which can suppress hallucinations and delusions without causing excessive sedation was highly welcomed. Many psychiatrists in those days thought that administration of the maximum dose of haloperidol, enduring possible adverse side effects, would promote the patients benefits. They believed that the anti-delusion/ hallucination effects of haloperidol might cause the suppression of pathological process of patients eventually leading to the recovery from schizophrenia. It was believed as the best regime of pharmacotherapy to use haloperidol as much as possible in combination with anticholinergic drugs, to control EPS and other side effects. In anticipation of antipsychotic effect, intravenous high-dose administration of haloperidol was carried out. It was difficult, however, to completely avoid EPS and other side effects in clinical settings. Aiming for the better anti-hallucination/ delusion effect, with less sedative action, several antipsychotics of butyrophenone were developed, such as pipanperone (Eisai, 1965), spiperone (Eisai, 1969), timiperone (Daiichi, 1984), and bromperidol (Yoshitomi, 1986) by Japanese pharmaceutical companies.

Antipsychotics of benzamide class, sulpiride, was developed in 1973, which was expected to have an activating effect on negative symptoms of chronic schizophrenic patients, rather than the anti-hallucination/ delusion effect, without sedative action. Sulpiride was frequently prescribed to chronic schizophrenia patients in hospital.

When these three classes of antipsychotics became available in psychiatric service, the combination of antipsychotics of the different class had become the conceptual strategy of pharmacotherapy to schizohrenia patients. Psychiatrists believed it to be the best strategy to select one antipsychotics with sedative action, one with anti-hallucination/ delusion action, and one with activating action, which naturally lead to the polypharmacy to schizophrenia patients. It has become common to prescribe several antipsychotics in combination of sedative phenothiazine derivative, anti-hallucination/ delusion butyrophenone derivative, and activating effect of benzamide. Japanese Pharmas developed sultopride (Daiichi) in 1989, mosapramine (Yoshitomi) in 1991, and nemopride (Yamanouchi) in 1991) as benzamide derivative compounds,

In 1996 the era of the second generation antipsychotics (SGA) started in Japan. Risperidone was introduced into Japan in 1996 as the first SGA with serotonine dopamine antagonist (SDA) action. Olanzapine (Eli-Lily), quetiapine (Astellas), and perospirone (Dainihon) were developed in 2001. Dainihon Pharma developed blonanserin in 2008. Once suspended development of clozapine due to its severe side effect of agranurocytosis was rechallenged and finally put into Japanese market in 2009. Otsuka Pharma, who successfully developed aripiprazole with Bristol-Myer-Squibb in US, finally introduced it to Japanese market in 2012.

## 4. First Generation Antipsychotocs (FGA) developed in Japan

Chlorpromazine, originally developed as an antihistamine drug by Rhone-Poulenc in 1950, was serendipitously discovered to have anti-psychotic effect by French navy surgian, Henri Laborit, in 1952, after using chlorpromazine (Hivernation®) to anesthesia of schizophrenic patients. Chlorpromazine was then widely used in Europe and USA as the medication to schizophrenia, opening the door of psychopharmacology in psychiatry (Lopez-Munoz 2005 ; Shen 1999).

FGAs currently used inJapan are listed in Table 1 in the order of their development. (Table 1). Chlorpromazine was introduced to Japanese market under the brand name of Contomin® by Yoshitomi Pharma in June 1955.The first report on clinical effectiveness of chlorpromazine was presented at the 54th Annual Meeting of Japanese Society of Psychiatry and Neurology in Sapporo by Isamu Sano (Osaka University Medical School) and Nozomu Suwa (Hokkaido University Medical School) in July 1957. Yoshitomi Pharma was sued by Novartis for violating patent owned by Novartis whose product was covered by inter-

Table 1　First Generation Antipsychotics Developed in Japan

| No. | name | class | date of marketing | registered name® | company name | **Available forms** (Powder, granule, tablet, capsule, liquid, and injection forms and dose is listed. The (　) of tablet shows the emboss of drug identifying code.) |
|---|---|---|---|---|---|---|
| 1 | Chlorpromazine | phenothiazine derivative | 1955.06 | Contomin® | Tanabe-Mitsubishi/Yoshitomi | Tablet 12.5 mg (Y/CO 12.5), 25 mg (YCO25), 50 mg (Y CO50), 100 mg (Y CO100) Injection 10 mg/2 mL/vial, 25 mg/5 mL/vial, 50 mg/5 mL/vial |
| | | | 1977.01 | Wintermin® | Shionogi | Powder 10% |
| 2 | Prochlorperazine | phenothiazine derivative | 1957.11 | Novamin® | Shionogi | Tablet 5 mg (095/5), Injection 5 mg/1 mL/vial |
| 3 | Perphenazine | phenothiazine derivative | 1960.05 | PZC® | Tanabe-Mitsubishi/Yoshitomi | Powder 1%, Tablet 2 mg (Y PZ2), 4 mg (Y PZ4), 8 mg (Y PZ8), Injection 2 mg/1 mL/vial |
| | | | 2002.01 | Trilafon® | Kyowa | Powder 1%, Tablet 2 mg (KW 352), 4 mg (KW 353), 8 mg (KW 355) |
| 4 | Levomepromazine | phenothiazine derivative | 1960.01 | Hirnamin® | Shionogi | Powder 50%, Powder 10%, Tablet 5 mg (003 5), 25 mg (004 25), 50 mg (005 50), Injection 25 mg/1 mL/vial |
| | | | 1963.01 | Levotomin® | Tanabe-Mitsubishi/Yoshitomi | Powder10, 50%, Granule10%, Tablet 5 mg (YLV5/5), 25 mg (YLV25/25), 50 mg (YLV50/50), Injection 25 mg/1 mL/vial |
| 5 | Fluphenazine | phenothiazine derivative | 1960.01 | Flumezin® | Tanabe-Mitsubishi/Yoshitomi | Powder 0.2%, Tablet 0.25 mg (Y/FL 0.25), 0.5 mg (Y/FL 0.5), 1 mg (Y/FL1) |
| 6 | Propericiazine | phenothiazine derivative | 1964.08 | Neuleptil® | Takada | Powder 10%, Tablet 5 mg (5NLP), 10 mg (10NLP), 25 mg (25NLP),Liquid 1% |
| 7 | Haloperidol | butyrophenone derivative | 1964.12 | Serenace® | Dainippon-Sumitomo | Powder 1%, Tablet 0.75 mg (312/0.75), 1 mg (317/1), 1.5 mg (313/1.5), 3 mg (318/3). Liquid 0.2%, Injection 5 mg/1 mL/vial |
| | | | 1978.04 | Linton® | Tanabe-Mitsubishi/Yoshitomi | Powder 1%, Tablet 0.75 mg (YLT/0.75), 1.5 mg (YLT/1.5), 2 mg (YLT/2), 3 mg (YLT/3), Injection 5 mg/1 mL/vial |
| 8 | Pipamperone | butyrophenone derivative | 1965.03 | Propitan® | Eisai | Powder 10%, Tablet 50 mg (112) |
| 9 | Spiperone | butyrophenone derivative | 1969.02 | Spiropitan® | Eisai | Tablet 0.25 mg (117), 1 mg (118) |
| 10 | Oxypertine | indole derivative | 1972.01 | Forit® | Daiichi-Sankyo | Powder 10%, Tablet 20 mg (114), 40 mg (113) |
| 11 | Sulpiride | benzamide derivative | 1973.08 | Dogmatyl® | Astellas | Powder 10 , 50 %, Tablet 50 mg (451), 100 mg (461), 200 mg (471), Capsule 50 mg (Dogmatyl/50 mg), Injection 50 mg/2 mL/vial, 100 mg/2 mL/vial |
| | | | 1979.05 | Miradol ® | Bayer | Powder 10, 50%, Tablet 50 mg (MPI 120), 100 mg (MPI 121), 200 mg (MPI 122) Capsule 50 mg (MPI 123/MPI 123) |
| | | | 1979.05 | Abilit® | Dainippon-Sumitomo | Powder 10, 50%, Tablet 50 mg (021/50), 100 mg (021/100), 200 mg (021/200), Capsule 50 mg (021/021) |
| 12 | Clocapramine | iminodibenzyl derivative | 1974.02 | Clofekton® | Tanabe-Mitsubishi/Yoshitomi | Granule 10%, Tablet 10 mg (YCF10), 25 mg(YCF25), 50 mg(YCF50) |
| 13 | Pimozide | diphenylbutylpiperidine derivative | 1974.04 | Orap® | Astellas | Powder 1%, Tablet 1 mg (111), 3 mg (131) |
| 14 | Zotepine | phenothiazine derivative | 1982.02 | Lodopin® | Astellas | Powder 10, 50%, Tablet 25 mg (621), 50 mg (651), 100 mg (611) |
| | | | 1995.10 | Losizopilon® | Tanabe-Mitsubishi/Yoshitomi | Powder 10, 50 %, Tablet 25 mg (62), 50 mg (65), 100 mg (03/100) |
| 15 | Timiperone | butyrophenone derivative | 1984.03 | Tolopelon® | Daiichi-Sankyo/Tanabe-Mitsubishi/Yoshitomi | Powder 1%, Tablet 0.5 mg (125/0.5), 1 mg (126/1), 3 mg (127/3), Injection 4 mg/2 mL/vial |
| 16 | Bromperidol | butyrophenone derivative | 1986.01 | Impromen® | Tanabe-Mitsubishi/Yoshitomi | Powder 1%, Tablet 1 mg (Y IP1/1), 3 mg (Y IP3/3), 6 mg (Y IP6/6) |
| 17 | Haloperidol decanoate | butyrophenone derivative | 1987.09 | Halomonth® | Dainippon-Sumitomo/Janssen Pharma | Long-acting Injection 50 mg/1 mL/vial, 100 mg/1 mL/vial |
| | | | 1987.09 | Neoperidol® | Janssen Pharma | Long-acting Injection 50 mg/1 mL/vial, 100 mg/1 mL/vial |
| 18 | Sultopride | benzamide derivative | 1989.04 | Barnetil® | Bayer/Dainippon-Sumitomo | Powder 50%, Tablet 50 mg (MPI 130), 100 mg (MPI 131), 200 mg (MPI 132) |
| | | | 2000.07 | Batil® | Tanabe-Mitsubishi/Yoshitomi | Tablet 50 mg (Y/BT 50), 100 mg (Y/BT 100), 200 mg (Y/BT 200) |
| 19 | Mosapramine | iminodibenzyl derivative | 1991.05 | Cremin® | Tanabe-Mitsubishi/Yoshitomi | Granule 10%, Tablet 10 mg (YCR10), 25 mg (YCR25), 50 mg (YCR50) |
| 20 | Nemonapride | benzamide derivative | 1991.05 | Emilace® | Astellas | Tablet 3vmg (021), 10 mg (022) |
| 21 | Fluphenazine decanoate | phenothiazine derivative | 1993.06 | Fludecasin® | Tanabe-Mitsubishi/Yoshitomi | Long-acting Injection 25 mg/1 mL/vial |

national patent of anti-psychotic action of chlorpromazine. Yoshitomi and Novartis had a long lasting court trial and Yoshitomi finally won the case based on its claim of chlorpromazine production patent, based on the Japanese patent rule in which newly synthesized compounds are protected by the patent of the synthesis method, not by the end product utility (at Osaka District Court on 11 September 1958). Owing to the great success and profits of chlorpromazine, Yoshitomi Pharma grew up to one of the leading companies producing antipsychotics. Shionogi Pharma bought the lisence of chlorpromazine from Novartis Pharma and put chlorpromazine on market under the brand name of Wintermin® in October of 1977.

Introduction of pharmacotherapy to schizophrenia dynamicaly changed the institutional management of schizophrenia patients and pushed the trend of liberalization of psychiatric hospitals in Japan. Medication was expected to have clinical use of 1) sedation to the patients in exitment, 2) anti-hallucination and –delusion effect to the patients with pathological experience, and 3) to improve negative symptoms of the chronic schizophrenia patients. A big success of chlorpromazine in Japanese psychiatric hospitals stimulated many pharmas including Yoshitomi and Shionogi to develop new phenothiazine derivatives with more clinical utility, such as perphenazine (1960), levomepromazine (1960), fluphenazine (1960), and propericiazine (1964).

In 1957 Paul Janssen in Belgium discovered haloperidol, a butyrophenone derivative of dopamine D2 antagonist effect, with strong anti-hallucination and anti-delusion potency. Haloperidol was put into Japanese market under the brand name of Serenace® by Dainihon Pharma in December 1964, and also under the name of Linton® by Yoshitomi in April 1978. Just like the case of chlorpromazine, many butyrophenone derivatives were develpoed by Japanese pharmas, including pipanperone (1969), spiperone (1969), timiperone (1984) and bromperidol (1986), which were modified from haloperidol with more D2 blocking activity and less blocking of other transmitter receptors expecting less adverse side effects.

Sulpiride had been used as drug for digetive ulcer and it was developed for the use to schizophrenis patients by Fujisawa Pharma with brand name Dogmatyl® in August 1973. (Fujisawa merged with Yamanouchi to become Astellas in 2005.) Sulpiride was also developed by Mitsui Pharma under the bame of Miradol® in May 1979 and by Dainihon Pharma under the name of Abilit® in May 1979. (Mitsui Pharma was merged by Bayer. Dainihon Pharma and Sumitomo Pharma were merged together to be Dainihon-Sumitono Pharma in October 2005). Sulpiride was well accepted by patients due to less sedative effect and widely prescribed to chronic schizophrenia patients expecting aleviation of negative symptom. Sultopride (1989) and nemonapride (1991) were benzamide derivatives developed by Dainihon in 1989 and Yamanouchi in 1991, respectively, for schizophrenia.

## 5. Second Generation Antipsychotocs (SGA) developed in Japan

The first generation antipsychotic drug (FGA) was effective for positive symptoms, but it has insufficient effects for negative symptoms. In addition, FGA has problems of side effects of extrapyramidal system (EPS) at high frequency, which makes the patients treated with FGA almost mandatory with these adverse side effects.

In 1984, Paul Janssen developed risperidone, a serotonin-dopamine antagonist (SDA), that blocks the dopamine D2 receptor and the serotonin 5-HT2A receptor, which was called “atypical antipsychotics”, and later “second generation antipsychotics (SGA)”.

The second generation antipsychotics (SGA) have significantly less side effects of EPS, and are widely used to controll positive as well as negative symptoms of schizophrenia patients. The SGAs currently used in Japn are listed in Table 2 (Table 2),

The era of SGA began in Japan by introduction of risperidone in 1996. The success of risperidone was followed by perospirone, olanzapine, quetiapine in 2001. Blonanserin (2008), clozapine (2009), paliperidone (2010), aripiprazol (2012), and asenapine (2016) are currently SGAs available in Japn at the present time.

Risperidone is a representative compound of serotonin-dopamine antagonist (SDA), which has suppressive action on 5-HT and dopamine neurons, with significantly less EPS side effects than most of FGA. Quetiapine has high affinity for the 5-HT2 receptor and is positioned as SDA having a weak affinity for 5-HT1, adrenergic $\alpha$1, $\alpha$2, and dopamine D1 receptors. Olanzapine, classified as a multi-acting receptor targeted antipsychotics (MARTA), has high affinity to dopamine D2, D3, D4 receptors, serotonin 5-HT2, 5-HT6 receptors, adrenaline $\alpha$1, and histamine H1 receptor. Aripiprazole acts as a partial agonist of

Table 2 Second Generation Antipsychotics Developed in Japan

| No. | name | date of marketing | registered name | company | **available forms** (Powder, granule, tablet, capsule, liquid, and injection forms and dose is listed. The ( ) of tablet shows the emboss of drug identifying code.) |
|---|---|---|---|---|---|
| 1 | Risperidone | 1996.06 | Risperdal® | Janssen Pharma | Powder 1%, Tablet 1 mg (JK 101), 2 mg (JK 102), 3 mg (JK 103), Oral Destructing Tablet 0.5 mg (JP 113), 1 mg (JP 107), 2 mg (JP 108), Liquid 1 mg/mL |
| 2 | Perospirone | 2001.02 | Lullan® | Dainippon-Sumitomo | Tablet 4 mg (057), 8 mg (058), 16 mg (DS 059) |
| 3 | Quetiapine | 2001.02 | Seroquel® | Astellas | Powder 50%, Tablet 25 mg (SEROQUEL 25), 100 mg (SEROQUEL 100), 200 mg (SEROQUEL 200) |
| 4 | Olanzapine | 2001.06 | Zyprexa® | Eli-Lily | Powder 1%, Tablet 2.5 mg (LILLY 4112), 5 mg (LILLY 4115), 10 mg (LILLY 4117), Oral Destructing Tablet 2.5 mg, 5 mg , 10 mg, Injection 10 mg/vial |
| 5 | Blonanserin | 2008.04 | Lonasen® | Dainippon-Sumitomo | Powder 2%, Tablet 2 mg (DS 032/2), 4 mg (DS 033/4), 8 mg (DS 035/8) |
| 6 | Risperidone | 2009.06 | Risperdal® Consta® | Janssen Pharma | Long-acting Injection 25 mg, 37.5 mg, 50 mg |
| 7 | Clozapine | 2009.07 | Clozaril® | Novartis Pharma | Tablet 25 mg (CLOZ25), 100 mg (CLOZARIL100) |
| 8 | Paliperidone | 2011.01 | Invega® | Janssen Pharma | Slow Release Tablet 3 mg (PAL3), 6 mg (PAL6), 9 mg (PAL9) |
| 9 | Aripiprazole | 2012.05 | Abilify® | Otsuka | Powder 1%, Tablet 3 mg (OG72), 6 mg (OG 71), 12 mg (OG 70), Liquid 0.1%, Oral Destructing Tablet 3 mg (3), 6 mg (6), 12 mg (12), 24 mg (24), Long-acting Injection 300 mg/vial, 400 mg/vial, 300 mg/1Syringe, 400 mg/1Syringe |
| 10 | Paliperidone | 2013.11 | Xeplion® | Janssen Pharma | Long-acting Injection 25 mg, 50 mg, 75 mg, 100 mg, 150 mg |
| 11 | Asenapine | 2016.05 | Sycrest® | Meiji-Seika Pharma | Sublingual Tablet 5 mg (5), 10 mg (10) |

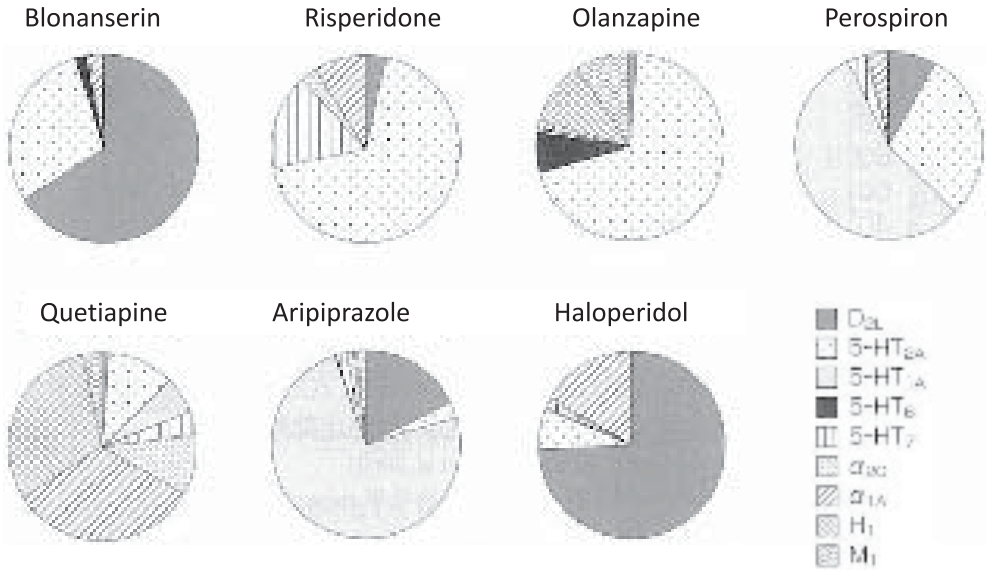


Figure 7 Different affinity of atypical antipsychotics to receptors in reference with haloperidol

dopamine D2 and 5-HT1A receptor and is also called as dopamine stabilizer (DSS) because it acts as an agonist in lower dose and as antagonist in higher dose.

SGAs have been well accepted in Japan, surpassing the use of the first generation drug (FGA), and a variety of forms were introduced. For example, Risperdal® can be prescribed as tablets (1 mg, 2 mg, 3 mg), fine grain ( 1 %), OD tablet (1 mg), and oral liquid (0.5 mL, 1 mL, 2 mL), Rispadal Constant® (50 mg) is availabe as sustained intramuscle injection.

## 6. Development of blonanserin, aripiprazol, and asenapin in Japan

The author will describe some inside stories concerning development of these antipsychotics by Japanese companies. Perospirone and blonanserin were developed by Dainihon-Sumitomo

and mainly used in Japan and in some Asian countries. Aripiprazol was also developed by Japanese company, Otsuka Pharma, and it has become a blockbaster antipsychotics with the great success in USA and Europe. Asenapin was the one developed not by Japanese pharma, but it was recently developud as the first sublingual tablet by Meiji-Seika Pharma.

**Blonanserin**

Perospirone was the first SGA produced by Japanese company. Since perospirone is regarded as a successor of tiospiperone developed by Bristol-Myers-Squibb, it might not be a real innovation by Japanese Pharma. Dainihon Pharma, however, continued to develop a new SGA, blonanserin, which can be regarded as a real original SGA compound produced by Japanese Pharma.

Dainihon Pharma had been engaged with CNS drugs for many yeons. In those days, Yoshitomi, Shionogi, and Dainihon were leading Japanese pharmaceutical companies specialized in CNS drugs in Japan. Dainihon Pharma introduced haloperidol to Japan and successfully put it on market under the trade name of Serenace® in December 1964. In addition, Dainihon was ready to develop clozapine in Japanese market, after completing clinical trials, which was filed for approval in 1975, even though it was not approved by Japanese authory due to unexpectedly high rates of agranulocytosis at that time. Against this backdrop, Dainihon Pharma worked on the development of new antipsychotics, searching for a compound with high affinity to D2 receptors, trying to develop antipsychotic drug superior to haloperidol.

Under such circumstances, stimulated by risperidone success by Janssen, a team of Dainihon Pharma launched a project of screening compounds with high affinity to 5-HT2 receptor. Although the initial lead compound showed high affinity to 5-HT2 receptor, it had relatively low affinity to D2 receptor. The research team of Dainihon Pharma had accumulated experience how to modify the compound to increase the affinity to D2 receptor from the experience of haloperidol development, and they gradually approached to the compound with high D2 affinity from the lead compound. Finally bronanserin (AD-5423) was synthesized in 1982, which has high D2 blocking activity and 5-HT2 blocking action, and little affinity to $\alpha$1, H1, M1 receptors, whose pharmocological profile was comparable to haloperidol.

Brananserin was shown to have strong 5-HT2 receptor and D2 receptor blockade in rat experiments. In a report using the cloned receptors from human tissue published in 2007, the affinity for D2 and D3 receptors is stronger than the affinity for the 5-HT2A receptor. Because of this nature, blonanserin is better called dopamine-serotonin antagonist (DSA) rather than SDA. A phase 1 study was conducted in August 1992, indicating that there is less influence on psychomotor function than haloperidol. In the phase 2A and phase 2B clinical trials, a dose of 8–24 mg / day showed nearly adequate clinical effectiveness and safety. Phase 3 trials began in March 1997, which was a double-blind controlled trial with haloperidol as the control. The blunanserin group showed 61.2% improvement while the haloperidol group showed 51.3% improvement, suggesting blonanserin has at least comparable clinical effectiveness with haloperidol. With this result, Dainihon applied for the approval of blonanserin to PMDA (Pharmaceuticals and Medical Devices Agency) in December 2001. Since it was a rule for PMDA to approve antipsychotics with the success of more than two pivotal clinical trials of double-blind study, the Japanese authorities declined the application and requested for another pivotal clinical trial to Dainihon.

Actually olanzapine had already been approved with the result of a single double blind study. The Japanese authories explained that the case of olanzapine was only an exception because many clinical trials abroad were available. In case of blonanserin which had no data of clinical trials outside Japan, at least two pivotal clinical trials were required. Then Dainihon was forced to challenge the second double blind study. The next double-blind study was carried out with risperidone as control, which was quite a challenging task because of the reputation of risperidone as a first line drug for schizophrenia. The double-blind study with risperidone as control was conducted at 59 centers in Japan from August 2003 to November 2004. The result of the second double-blind study successfully demonstrated the comparable clinical effectiveness of blonanserin with risperidone, and blonanserin was launched as Lonasen® in April 2008.

**Aripiprazol**

Otsuka Pharmaceutical, established in Tokushima City in 1921, is a pharma specialized to infusion liquid for a long time, and it was relatively new to launch the institute for drug development. It is a remarkable achievement of Otsuka Insti-

tute to successfully develop four compounds into the market within a short period from its start in 1971 ; Carteolol (Mikelan®) in 1980, procalerol (Meptin®) in 1980 ; cilostazol (Pretal®) in 1988, and rebamipide (Mucosta®) in 1990, all of which are quinolinone derivatives with carbostyril structure. With the success of these drugs, Otsuka had decided to launch a project for developing drugs from quinolinone derivatives. The project started to develop antihistamine drugs from quinolinone derivatives having carbostyril skeleton having only peripheral effects not entering into the CNS. During the process, it turned out that some derivatives actually cause CNS effects entering inside the brain, and they have changed their target to the development of antipsychotics. After some trial and errors, OPC-4392 was selected in 1980, which was shown to have agonistic action to DA receptors. The agonistic action to DA system was shown to be caused by selective dopaminergic action at presynapse site (Sasa, 1988). In those days Arvid Carlsson had already discovered autoreceptors present at presynaptic sites of the central dopaminergic pathway (Carlsson, 1972), and Roth demonstrated that this DA autoreceptor suppresses DA synthesis, release, and ignition in an inhibitory manner (Roth, 1979). Supported with these academic findings, a P1 clinical trials of OPC-4392 was launched in November 1983. The P1 study completed successfully, and it was advanced to P2 and P3 studies at institutions in Japan. The results of the P2 and P3 trials, however, were far below than expected. Clinical effectiveness of OPC-4392 was studied by a comparative study with sulpiride in one P3 study and with chlorpromazine in the second P3 trial. The development of OPC-4392 was discontinued in 1989 because it was not possible to achieve satisfactory results in any of the P3 trials.

The failure of OPC-4392 has led to the success of the subsequent compound OPC-14597 (aripiprazol). Otsuka team's rationale was to synthesize a compound having the same DA autoreceptor agonistic action as OPC-4392 and a strong post-synaptic antoagonistic effect to post synaptic D2 receptors, which can cause good effect to the negative syptoms by the former, and good effects to the positive symptoms by the latter. Oshiro and colleagues used the suppression action of apomorphine-induced stereotypy for the postsynaptic D2 receptors and the increase in DOPA synthesis by gamma-butyrolactone as an indicator for the pre-synaptic DA autoreceptor agonism. Considering the later development of aripiprazol, it is the reason of success that they adopted the screening process of pursuing the two effects at the same dose, leading to finding of the proper intrinsic activity of aripiprazol (Oshiro, 1998).

Two compounds were selected from the chemical library between 1985 and 1986. After chemical modification pocess from these two compounds, a lead compound having the post-synaptic D2 receptor antagonistic action and the presynaptic autoreceptor agonistic action at the same dose was finally synthesized., and after the study of manufacturing method and evaluation of ADME, OPC-14597 (Aripiprazol) was synthesized in February 1987.

Otsuka soon started development of aripiprazol in the United States. Clinical trials were carried out by Otsuka America and they found in two placebo controlled trials that aripiprazol shows good improvement of positive symptoms, and also of negative syptomsin, with extremely few EPS, and decrease in blood prolactin level. In those days, Bristol-Myers-Squibb was eager to develop new antipsychotics, and Otsuka and Bristol-Myers-Squibb agreed for the contract of co-development of aripiprazol in September 1999. Then the development of aripiprazol progressed rapidly and steadily by the collaboration of these two companies, and aripiprazol was approved by FDA in 2002. Approval of aripiprazol was delayed partly due to the new regulational change in Japan, which requires observing the new GCP guidelines, and aripiprazol was approved by PMDA in 2012.

**Asenapine**

Asenapine (Cyclest®) is the most recent antipsychotics developed in Japan. Asenapine is a drug belonging to MARTA like olanzapine (zyprexa®), clozapine (Clozaril®), quetiapine (Seroquel®), having an antagonistic effect on serotonin 5-HT2 receptor and dopamine D2 receptor. Asenapine was approved by European Union (EU) in September 2009 and in the US in September 2010, Pfizer sells it under the product names of Geodon® / Zeldox®, in more than 61 countries worldwide.

Asenapine was developed by Meiji-Seika Pharma with the goal of controlling acute symptoms for schizophrenia, preventing recurrence of symptoms during maintenance treatment period, and prevention of recurrence as well as improvement of QOL of patients. Asenapine maleate (trade name Cyclest® sublingual tablet 5 mg, 10 mg) was approved in March 2016 as the first form

of a sublingual tablet of antipsychotropics. Asenapine has a large initial pass effect when absorbed in the gastrointestinal tract, and is metabolized by the liver. Therefore, asenapine was developed as a rapidly disintegrating sublingual tablet which is quickly absorbed from the oral mucosa, trying to keep the enough bioavailability. Another characteristics of asenapine is that its effective dose can be administrated from early treatment while most of existing SGAs to be gradually increased its dose to reach an effective dose in order to reduce adverse events.

Asenapine has been shown to have comparable efficacy as other SGAa and similar adverse side effect profile such as glucose metabolic side effects, hyperprolactinemia, QTc prolongation and little anticholinergic side effects. In addition, it can be used for excitement and irritability with schizophrenia patients, because Tmax of acenapine sublingual tablet is as short as about 1 hour. The administration method as a sublingual tablet was first used clinically as a therapeutic agent for schizophrenia, because the bioavailability of sublingual administration is about 35%, whereas if swallowed, is less than 2 %. In clinical practice, it is necessary to give the instruction how to intake sublingual tablets seeking understanding and cooperation to drug therapy, which may be utilized to improve the therapeutic relationship aiming for sufficient communication between clinicians and patients.

## 7. Overview of SGAs Use in Japan

The list of pharmacologic profiles of eight SGAs used currently in Japan are listed in Table 3, together with those of two FGAs for comparison (Table 3). Based on the pharmacological profile, they show specific side effect profiles as shown in Table 4.

Pharmacotherapy for schizophrenia requires long-term treatment period often extended over several years, and adherence to pharmacotherapy is a major challenge in clinical settings. For that reason, sustained long-term depot preparation has been devised. Risperdal・Consta® is administered once every two weeks as intramuscular injection and Zeplion® (sustained release formulation of paliperidone) once every 4 weeks have been developed as intramuscular injection preparation. Asenapin has been developed as a sublingual tablet, and blonanserin is being developed as a transdermal absorption patch.

SDAs have been rapidly expanded its applica-

Table 3 Pharmacological profiles of second generation antipsychotics used in Japan

| class | compound | brand name | year on market | D2 | 5-HT2A | 5-HT2C | α1 | H1 | M1 |
|---|---|---|---|---|---|---|---|---|---|
| FGA | chlorpromazine | Contomin® | 1955 | +++ | ++ | ++ | ++++ | ++++ | ++++ |
| FGA | haloperidol | Serenace® | 1964 | ++++ | ++ | — | +++ | — | — |
| SDA | resperidone | Rispadal® | 1996 | ++++ | ++++ | ++ | +++ | + | — |
| SDA | perospiron | Lullan® | 2001 | ++++ | ++++ | ++ | ++ | ++ | — |
| MARTA | quetiapine | Seroquel® | 2001 | + | ++ | — | +++ | ++ | + |
| MARTA | olanzapine | Zyprexa® | 2001 | +++ | ++++ | ++ | ++ | +++ | +++ |
| SDA | blonanserin | Lonasen® | 2008 | ++++ | ++++ | ++ | — | — | ++ |
| SDA | parriperidone | Invega® | 2011 | ++++ | ++++ | ++ | +++ | + | — |
| DSS | aripiprazol | Abilify® | 2012 | ++++ | +++ | ++ | + | + | — |
| MARTA | asenapine | Sycrest® | 2016 | ++++ | ++++ | ++++ | +++ | +++ | — |

Table 4 Adverse side effects of second generation antipsychotics used in Japan

| class | compound | brand name | year on market | EPS | prolacti-nemia | constipation dry mouth | dizziness | sleepiness | weight gain |
|---|---|---|---|---|---|---|---|---|---|
| FGA | chlorpromazine | Contomin® | 1955 | ++ | + | +++ | +++ | +++ | ++ |
| FGA | haloperidol | Serenace® | 1964 | +++ | ++ | — | ++ | + | — |
| SDA | resperidone | Rispadal® | 1996 | ++ | +++ | — | ++ | + | ++ |
| SDA | perospiron | Lullan® | 2001 | + | + | — | + | + | + |
| MARTA | quetiapine | Seroquel® | 2001 | — | — | + | ++ | ++ | ++ |
| MARTA | olanzapine | Zyprexa® | 2001 | — | + | ++ | + | ++ | +++ |
| SDA | blonanserin | Lonasen® | 2008 | ++ | + | + | — | — | — |
| SDA | parriperidone | Invega® | 2011 | + | +++ | — | + | — | + |
| DSS | aripiprazol | Abilify® | 2012 | + | — | — | — | — | — |
| MARTA | asenapine | Sycrest® | 2016 | + | + | — | + | ++ | + |

tion to many different psychiatric disorders. In addition to schizophrenia, aripiprazole has been approved for manic state of bipolar disorder, augment therapy for treatment of depression with antidepressants, and adaptation to the irritability of autism. Quetiapine is recommended for treatment of acute and maintenance periods of bipolar disorder in overseas guidelines in addition to schizophrenia (Grunze, 2013 ; Yatham, 2013), and this indication was approved in Japan in 2017.

The rapid expansion of SGAs indication is of course welcomed by patients which has opened more availability of medication to the disorder. It is true, however, a variety of SDAs indication may mislead the guideline for clinicians based on the simple drug to disorder relationships. SGAs are shown effective not only for schizophrenia but also for many pathological conditions that have been regarded as separate and independent diseases such as bipolar disorder, depression, and autism. It is no more valid to speculate one transmitter action is indicated for the remdy of one disorder in psychiatry. This experience has also caused a major change in the positioning of antipsychotics itself. It is no more possible to speculate one-to-one correspondence between the drug's pharmacological action and the target diseases, such as antipsychotics against schizophrenia, antidepressants against depression, mood stabilizers for bipolar disorder, and anxiolytics for anxiety disorders. New positioning and classification of psychotropic drugs including antipsychotics as a whole has become necessary, and new naming and classification of psychotropics should be considered for the better practice in psychiatric pharmacotherapy.

## 8. Antipsychotocs under development in Japan

Some SGAs developed in Europe and USA are under development in Japan. The compounds already approved oversears are briefly reviewed mensioning the present situation of development in Japan.

**Ziprasidone (Geodon®)**

Ziprasidone has selective blocking of serotonin 5-HT2A and dopamine D2 receptors, partial agonist action of 5-HT1A receptor, partial antagonist action of 5-HT2C, 5-HT1D receptor (Seeger, 1995), which was first approved in Sweden in 1998. In the United States, the FDA authorieis concerned about QT prolongation, and extra clinical trial was required by FDA to be finally approved. In addition to the D2 receptor blocking effect, the 5-HT2A receptor blocking action is considered to alleviate the positive symptom of schizophrenia, but the involvement of the 5-HT2A blocking effect is under discussion. 5-HT2A and 5-HT2C blocking action, and 5-HT1A stimulating action may be involved in improvement of negative symptoms. Although weak adrenergic $\alpha$1A, $\alpha$1B receptor action may be involved in orthostatic hypotension, there is little anticholinergic side effect because it has no effect on mACh receptor. Sedative action is due to serotonin and dopamine blocking action (Monti, 2010 ; Salmi, 2000).

Ziprasidone was put into market by Pfizer under the trade name of Geodon in US in February 2001. In addition to schizophrenia, new indications have been approved to bipolar manic phase and mixed phase in US. Ziprasidone has the same efficacy as existing SGAs, but it is characterized by less side effects such as weight gain and increase in blood glucose level. Intramuscle injection has been approved for acute symptoms of anxiety with schizophrenia patients. Ziprasidone is listed as the first-line drug in the schizophrenia treatment guideline in the United States because of less side effects of drowsiness and headache (>10%), and the least weight gain among SGAs as shown in Figure 8 (Figure 8)

According to the report in 2013, zibrasidone is ranked almost in the middle of 15 SGAs available. It is 15% more effective than lurasidone and iloperidone, almost equivalent to chlorpromazine and asenapine, haloperidol, and is 9–13% less effective than quetiapine and aripiprazole (Leucht, 2013). Currently it is on market in 83 countries, and Meiji Seika Pharma is now developing it in

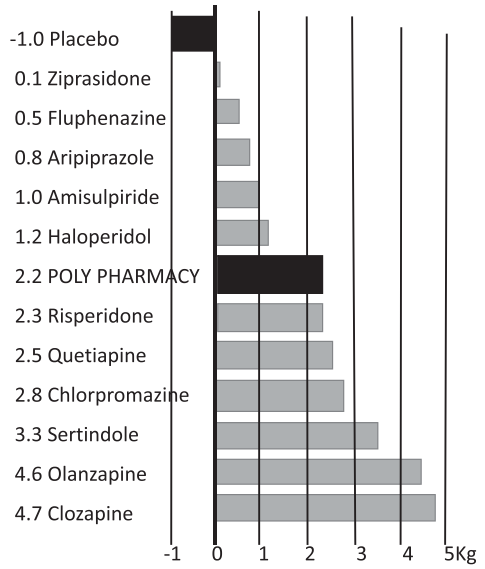


Figure 8 Weight gain from antipsychotic use for 2.5 months

Japan.

**Iloperidone (Fanapt®, Zomaril®)**

Iloperidone has high affinity to serotonin 5HT2A receptor (Ki value ; 5.6 nM), dopamine D2 receptor (6.3 nM), dopamine D3 receptor (7.1 nM), noradrenaline alpha 1 receptor (0.36 nM), dopamine D4 receptor (25 nM), serotonin 5HT6 receptor (43 nM), 5HT7 receptor (22 nM) serotonin 5HT1A (168 nM), but has no affinity for dopamine D1, and histamine H1 receptor. Iloperidone showed remarkable effects in animal studies and it was demonstrated that iloperidone improves prepulse inhibition (PPI) attenuation in schizophrenia patients, and in PCP-induced psychotic patients (Barr, 2006). It was approved by FDA in June 2009 after demonstrating significant clinical efficacy compared to placebo in 4 RCT trials. In the report of 2013, Iloperidone is evaluated almost equivalent to that of zibrasidone, chlorpromazine, acenapine among 15 SGAs (Leucht, 2013). Clinical development in Japan is not planned at present.

**Lurasidone (Latuda®)**

Lurasidone is an SGA discovered and developed by Dainihon-Sumitomo Pharma, and it is already widely used in Europe and in USA. Based on such achievements, clinical development in Japan has been underway now.

In US and Canada, lurasidone was approved for schizophrenia in October 2010, for bipolar type 1 depression in July 2013, for childhood schizophrenia in January 2017, and for childhood bipolar type 1 depression in May 2017. As of May 2017 it is sold in UK, Switzerland, Denmark, Norway, the Netherlands, Finland, Sweden in Europe. Lurasidone is widely accepted in the world, and the sales of lurasidone recorded more than 100 billion Yen in 2015 fiscal year.

Lurasidone blocks dopamine D2, serotonin 5-HT2A, serotonin 5-HT7, and it has partial action to serotonin 5-HT1A receptor. Since it does not act on histamine receptors and muscarinic receptors, risk of extrapyramidal symptoms is significanly less than other SGAs.

Development of lurasidone in Japan is behind the schedule. Phase 3 clinical trials (PASTEL study) conducted in Japan did not produce the enough supports. In the study, 439 patients were randomly assigned to the three groups ; lurasidone 40 mg/day, 80 mg/day, and placebo groups for 6 weeks. Although the results of the primary endpoint of positive and negative symptom evaluation scale (PANSS : Positive and Negative Syndrome Scale) showed a tendency of improvement compared to placebo (−13.1) (40 mg : −17.9, 80 mg : −17.3), no statistically significant difference was observed. However, when the analysis population was changed to ITT (n=450), a significant difference was recognized with 40 mg/ day group ; −17.7 with 80 mg / day administration group : −16.8 for 40 mg/day group, and +11.9 for placebo group.

Currently, another Phase 3 trial is undergoing scheduled to be completed in 2018. The Phase 3 trials are also being conducted for bipolar type 1 depression, and for maintenance of bipolar disorder. Dainihon-Sumitomo Pharma apparently plans to apply for the simultaneous approval in 2019 for schizophrenia and for bipolar disorder.

Based on its pharmacological properties, lurasidone is expected to be effective against positive symptoms of schizophrenia, with low risk of cardiovascular events 5-HT7, and 5-HT1A actions are thought to contribute to cognitive improvement of depression and schizophrenia. Improvement in cognitive function by MCCB has been confirmed in CogState in PEARL trial in US. The improvement of cognitive function by lurasidone in combination with cognitive behavior therapy was demonstrated with bipolar disorder by ISBD-BANC. Lurasidone is suggested to be an agent useful for improving cognitive function for psychiaric patients.

**Brexpiprazole (Rexulti®)**

Aripiprazole (Abilify®) developed by Otsuka Pharma was approved in many countries around the world because of its high efficacy to schizophrenia, with fewer side effects and wide range of further indications. In 2012 it was ranked as the top sales drugs in US. Brexpiprazole, also developed by Otsuka Pharma, is structurally similar to aripiprazole. Brexpiprazole was approved by FDA for schizophrenia as well as for augmentation to treatment-resistant depression in July 2015 and has been marketed under the trade name of Rexulti®.

Brexpiprazole's pharmacological action is similar with that of aripiprazole, acting as a partial agonist at 5-HT1A receptor and dopamine D2, D3 receptor (Maeda, 2014), but brexpiprazole has a slightly stronger inhibitory effect than activating effect on these receptors compared to aripiprazole. It has also inhibitory effects on 5-HT2A, 5-HT2B, 5-HT7 receptor, adrenaline $\alpha$1A-, $\alpha$1B-, $\alpha$1D-, $\alpha$2C-receptor, but has no effect on acetylcholine receptor. Based on these pharmacological properties, brexpiprazole, strongly binding to the dopamine D2 receptor and serotonin

5HT1A receptor, acts as a partial agonist. Serotonin-Dopamine Activity Modulator ( SDAM) has been proposed as a new mechanism of action of brexpiprazole, acting as an antagonist for serotonin 5HT2A receptor and dopamine D2 receptors. Brexpiprazole is under development by Otsuka in Japan.

**Cariprazine (Vraylar®)**

In general, patients with schizophrenia whose main symptom is negative symptoms are difficut to be treated by existing antipsychotics. Cariprazine has been developed targeting negative symptoms of schizophrenia. Cariprazine has a partial agonist action on dopamine D3, and D2 receptors, which is developed by Gedeon Richter in Hungary. Cariprazine's unique feature is that the affinity for D3 receptor is stronger than that of D2. In US, the effectiveness of cariprazine was investigated in three clinical trials with 1,754 schizophrenia patients for 6 weeks in comparison with the placebo. The efficacy against bipolar disorder was also confirmed by three clinical trials. Cariprazine was approved by FDA for adult schizophrenia and bipolar disorder in September 2015, and it was put on the market as Vraylar®.

Recently, the results of Phase 3b trial of cariprazine were reported in Lancet, in which cariprazine and risperidone were administered for 26 weeks to 461 chronic schizophrenia patients in Europe, and the improvement was measured with PANSS–FSNS. The results demonstrated significant improvement of 8.9 points with cariprazine and −7.44 points with risperidone, showing cariprazine improves the negative symptom more than risperidone (Nemeth, 2017). In Japan, Mitsubishi-Tanabe Pharma is developing cariprazine for the use of schizophrenia.

## 9. Novel antipsychotics aiming for new mechanisms of action and targets

Relatively new compounds, which are not yet approved in any countries, will be described briefly in this section.

**Bitopertin**

Bitopertin is a drug having glycine reuptake inhibitory action developed by Roche as a combination drug for treatment of schizophrenia. Bitopertin increases the glycine concentration in the synaptic cleft by the action of a glycine transporter (GlyT1) inhibitor (Umbricht, 2014). Since glycine acts as an agonist of the NMDA receptor, it is mediated through NMDA receptors in schizophrenia and an action to improve the malfunction of the glutamate signal may be considered.

In the P-2 trial, negative symptoms of schizophrenia patients showed improvement after 8 weeks administration, and 83% of patients who received the drug reported improvement of negative symptoms (Umbricht, 2010). Sufficient results, however, were not obtained in the P-3 clinical trial reported in 2014. Development as an initial therapeutic agent for schizophrenia is not supported, and Roche has decided to continue developing as the drug for obsessive-compulsive disorder (Umbricht, 2014).

**Encenicline (EVP-6124, MT-4666)**

Encenicline is a partial agonist for acetylcholine $\alpha 7$ nicotinic receptor. In the P-2a clinical trial, 21 patients with schizophrenia were treated with encenicline for 21 days and indices related to cognitive function were examined, in which encenicline showed improvement of P 300 and mismatch negativity in dose-dependent manner (Preskorn, 2014). Based on these results, Phase 3 clinical trials were conducted to improve cognitive function of schizophrenia patients, but it was temporarily suspended because of gastrointestinal adverse side effects in 2015.

**Zicronapine, (Lu AF 356152)**

Zicronapine is an atypical antipsychotics having an antagonistic effect on D1, D2, 5HT2A receptors developed by Lundeck. A significant clinical effect was reported in the P2 trials compared with olanzapine and placebo, but in 2014 Lundbeck announced the suspension of zicronapine development and the switch to Lu AF 35700, a prodrug of zicronapine, which shows a better drug profile than zicronapine.

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