ORIGINAL ARTICLE

Pharmacotherapy of Schizophrenia: The American Current Status

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Abstract. This is a review paper covering the American current status of pharmacotherapy of schizophrenia. The author lists all available antipsychotic agents on the market in the United States and describes the American prescribing pattern of antipsychotic agents. This includes a brief history of antipsychotic use in America, acute treatment and chronic maintenance with antipsychotic drugs, the recent advent of atypical antipsychotic agents, and management of antipsychotic-induced side-effects. The characteristics of prescribing American antipsychotics in America are described, and they are then compared with Japanese prescribing practices. The author also makes brief remarks about the uncovered issues in antipsychotic pharmacotherapy and about atypical antipsychotic agents in the context of the future pharmaceutical development. (Keio J Med 43 (4): 192–200, December 1994)

Key words: antipsychotics, atypical antipsychotics, psychopharmacology, American prescribing pattern, schizophrenia

Introduction

This paper is a brief review which deals with research findings, clinical issues and strategies in the pharmacological treatments for “Schizophrenia and Other Psychotic Disorders” as one of new 15 DSM-IV Axis I diagnostic categories.¹ The diagnoses (and their codes) include schizophrenia (395.xx, 5 types), schizophreniform disorder (395.40), schizoaffective disorder (295.70), delusional disorder (297.1), brief psychotic disorder (298.8), shared psychotic disorder (297.3), psychotic disorder due to [a general medical condition] (293.xx), substance-induced psychotic disorder (refer to substance-related disorder for substance-specific codes), and psychotic disorder not otherwise specified (298.9).

This paper is intended as a companion paper similar to two previous papers in The Keio Journal of Medicine on the topic of pharmacotherapy of depression² and of alcoholism,³ respectively. This article deals only with important and updated relevant basic science data and clinical studies to familiarize Japanese colleagues with the state-of-the-art pharmacotherapy of schizophrenia in the United States.

Available Antipsychotic Agents on the US Market

Table 1 is a list of antipsychotic agents which are commonly prescribed in the US. The numbers of potency equivalent dose in mg listed in Table 1 are from various sources and are often inconsistent. Promazine and reserpine are available in America but are omitted from the list due to their inferior antipsychotic effects. Prochlorperazine and thiethylperazine are marketed in the US as antiemetic agents since their utility as antipsychotic agents is questionable. Those agents which are available in Japan are also indicated in Table 1. But thiothixene is spelled tiotixene, and loxapine is called clotiapine on the Japanese market. Those available in Japan but not on the U.S. market are levomepromazine, propericiazine, perazine, thioproperazine, zotepine, fluoropipamide, spiperone, moperone, timiperone, bromperidol, caripramine, clocapramine, oxypertine, sulpiride, sultopride, and others.

The mechanism of how an antipsychotic works is still not completely understood. Typically, they are all potent dopamine (DA) receptor antagonists which block DA transmission in all CNS DA systems. DA neuron systems include mesolimbic/cortical, nigrostriatal, tuberohypophyseal, retinal, olfactory bulb, incertohypothalamic,

Table 1 Antipsychotic Agents Available in the United States

Drugs	Potency Equivalent Dose (mg)
Phenothiazines	
Aliphatic Groups	
Chlorpromazine ^{a,c,h}	100
Triflupromazine ^{d,h}	25–50
Piperazine Groups	
Perphenazine ^{d,h}	8
Trifluoperazine ^{d,h}	5
Fluphenazine ^{b,d,h}	2
Acetophenazine	25
Piperidines	
Thioridazine ^{c,h}	100
Mesoridazine ^c	50
Thioxanthines	
Aliphatic Group	
Chlorprothixene ^b	50
Piperazine Group	
Thiothixene ^{a,d,h} (Tiotixene)	4
Dibenzoxazepines	
Loxapine ^{a,h} (Clotiapine)	15
Clozapine ^c	50
Dihydroindole	
Molindone ^d	15
Butyrophenone	
Haloperidol ^{a,h}	2
Droperidol ^{a,g}	1
Diphenylbutylpiperidine	
Pimozide ^{f,h}	1–2
Benzisoxazol	
Risperidone ^e	0.5

^a Available in injectable form; ^b Available in depot injectable form; ^c Low-potency antipsychotic; ^d High-potency antipsychotic; ^e Atypical antipsychotic; ^f Marketed for Tourette's syndrome; ^g Marketed for use in anesthesia; ^h Available in Japan; Drug name in parenthesis being the spellings used in Japan.

periventricular, and diencephalospinal systems.^{4,5} The first two DA neuron systems are located in mesotelencephalic areas (A10 in ventricle tegmental area and A9 in substantia nigra) and are the largest DA systems of all afore-mentioned eight systems.⁴ The postsynaptic receptor blockage that diminishes DA activity in the mesolimbic/cortical DA system is implicated in clinical improvement of positive psychotic symptoms including delusions, hallucinations, disorganized speech (e.g. frequent derail-

ment or incoherence), or grossly disorganized or catatonic behaviors.¹ Clinically, the receptor blocking property of other DA systems due to antipsychotic agents is implicated in the cause of side-effects such as movement disorders (from involvement in A9) neurons, weight gain, abnormality of thermoregulation and elevated prolactin level (from involvement in D12–14 in hypothalamus). Because of the side-effects that produce movement disorders, older conventional antipsychotic agents also earned the name “neuroleptics.” In addition, the DA receptor blockage in the area postrema (D4) produces antiemetic effects which usually do not have any clinical significance except in rare cases of episodic or persistent vomiting following withdrawal of an antipsychotic after its long-term use.^{6,7}

Most antipsychotics (especially those of low-potency agents) are not pure and are involved in the blockage of multiple neurotransmitter systems. These kinds of characteristics made researchers at Rhone-Poulenc in France give chlorpromazine the trade name Largactyl, meaning “large involvement.”⁸ Besides the DA system, antipsychotics have major involvements in α_1 adrenergic, histaminergic, muscarinic cholinergic, and serotonergic (5-HT) systems. Because of the involvements in neurotransmission, there are side-effects of orthostatic hypotension, sedation, and cardiac conduction abnormalities. The calcium channel blocking effect from low-potency antipsychotics (especially thioridazine) is thought to be the cause of male ejaculatory disturbances and female orgasmic disorders.^{9–11} A more detailed review of antipsychotic-induced side effects and their management is covered later in this article.

In Table 1, clozapine, risperidone (in low dosage level) and molindone (to some extent)¹² are classified as atypical antipsychotics. Molindone is not well-accepted as an atypical antipsychotic nowadays because its preferential DA autoreceptor inhibition does not show its significant selectivity of the DA mesolimbic/cortical system as compared with clozapine and risperidone. For the same reason, thioridazine is not considered as an atypical antipsychotic agent. Unlike haloperidol, thioridazine's lack of extrapyramidal symptoms (EPS) is thought to be from its high intrinsic antimuscarinic activity,¹³ which is similar to the concept that a combination pill of haloperidol plus an anticholinergic drug is equal to a pill of thioridazine. Differing from typical antipsychotics, atypical antipsychotic agents appear to act selectively on the mesolimbic/cortical DA systems in preference to the nigrostriatal (and maybe the tubero-infundibular) DA systems. Atypical antipsychotics also might improve negative symptoms (flattening affect, alergia or avolition)^{1,14} which might be refractory to treatment with typical antipsychotic agents.¹⁵

The American Pattern of Using Antipsychotic Agents

A brief history of prescribing antipsychotic medications in the US

Delay and Deniker in 1952 did the first successful clinical trial of chlorpromazine in chronic psychotic patients in France. After its introduction in America, the major American clinical research activity in treating schizophrenia from late 1950's to late 1970's had been preoccupied with the efficacy of chlorpromazine and other antipsychotic agents. Every newly introduced drug needed clinical controlled studies to determine whether it was better than or as good as chlorpromazine in improving psychotic symptoms/signs or improving the clinical rating scales.

In the absence of any proven controlled studies that high dosages of a neuroleptic are more effective than low dosages of the same agent,¹⁶ the major clinical research focus in the US from late 1970's to mid-1980's was on the use of high dosages of neuroleptics. After the late 1980's, the prescribed dosage levels of antipsychotic agents have been reduced to no more than 20 mg/day of haloperidol or the equivalent dosages of other antipsychotics. This prescribing pattern started after the research findings found that the high dosage levels of an antipsychotic do not give any additional benefit but do produce more side-effects, especially movement disorders.^{16,17} Thanks to the promotions by manufacturers of benzodiazepines in the past 15 years, psychiatrists started to sedate agitated disturbed patients with a high dose of a benzodiazepine plus a reasonable daily dose of a neuroleptic rather than using rapid "neuroleptilization" (cf. digitalization in concept) dosing techniques with parenteral neuroleptics such as chlorpromazine,¹⁸ haloperidol,¹⁸⁻²¹ thiothixene,^{19,21} and loxapine.²¹ At the same time, low-potency neuroleptics which were used preferably to sedate acute psychotic patients, have been substituted with high-potency neuroleptics and a benzodiazepine. As compared with low-potency neuroleptics, high-potency neuroleptics often have purer DA blocking properties and are less likely to block other CNS neurotransmissions.²²⁻²⁴ Besides enhancing the activation of *r*-aminobutyric acid_A (GABA_A) receptors which open chloride channels and produce sedation,³ a benzodiazepine has minimal involvement in other CNS neurotransmission systems.

Acute treatment and chronic maintenance with antipsychotic drugs

To treat patients in an acute psychotic state (either from the first episode of a newly developed schizophrenia or from one of the relapses in an acute exacerbation of a previously remitted condition), the psychiatrists are free

to choose an antipsychotic or to just place the patients back on an agent which was effective in the past. The choice of deciding an antipsychotic agent is based on the clinician's comfort with a particular antipsychotic, the avoidance or the invitation of expected side-effects, factors related to the patient's medical history, family history of response and tolerance to specific agents, the availability of a particular drug administration route such as short- or long-acting depot intramuscular injections (as indicated in Table 1), and often financial considerations. Similar to the guidelines of antihypertensive treatment,²⁵ antipsychotic therapy must be tailored to the individual patient. Small differences in efficacy (if any) may be less important than differences in quality of life or cost. From results of controlled studies, all antipsychotics have been proven equally efficacious in their antipsychotic properties,^{16,26-29} with the possible exception of clozapine.¹⁵

After the patient's disturbed behavior is under control, the daily antipsychotic dosage is gradually adjusted to a minimal but adequate dose,³⁰⁻³² administered on a once (preferably) or twice daily schedule.³³ Depot decanoate medication is indicated if the patient has a previous history of relapse due to poor compliance with antipsychotics and inadequate medication supervision. The patient's existing oral medication is changed to either fluphenazine or haloperidol. Then, a dose of long-acting depot of either drug is given.

The patients who received active maintenance therapy with antipsychotic agents show 75% relapse prevention at one year in comparison with only 20% for those who received a placebo.³⁴ Patients continue their maintenance antipsychotic therapy with regular follow-up by psychiatrists who evaluate their mental state for symptom remission, medication side-effects, and psychosocial stressors. The patient's antipsychotic dose is increased or decreased according to all these clinical determinants. The psychiatrist should make an effort to reduce the patient's neuroleptic dose if the patient's mental condition permits it. A recent paper describing a meta-analysis of 22 published randomized control trials concluded that no incremental clinical improvement was found at doses above 375 mg/day equivalent of chlorpromazine while a significant increase in adverse side-effects was observed.³⁵ This suggestion was also made by the British Royal College of Psychiatrists's consensus statement.³⁶

In maintenance therapy, sometimes "target" or "intermittent" medication strategy is also used in selective stable outpatients to avoid receiving an unnecessary cumulative dose of antipsychotics.³⁷⁻³⁹ With this strategy, patients in a stable remission state under maintenance antipsychotic therapy for a period of time, are withdrawn completely from antipsychotic agents. As expected, the antipsychotic-free patients have higher relapse rates than those who receive a reduced or standard

dosage of antipsychotic agents.⁴⁰ As soon as prodromal symptoms and signs of relapse emerge, the patients are immediately put back on their previously documented adequate neuroleptic doses before full-blown psychosis develops. The prodromal signs and symptoms are sleeping disturbances, difficulties in concentration, changes of energy level, and early psychotic manifestations such as delusions or hallucinations.⁴¹ It is important to note that some patients do relapse despite taking medication compliantly,⁴⁰ and that psychiatrists, families, and the patients themselves need to detect early prodromal signs and symptoms as soon as possible.

Usually, American psychiatrists do not check the serum neuroleptic level routinely unless there is a need to differentiate whether the patient suffers from neuroleptic side-effects or from psychotic decompensation.⁴² There are no well-defined antipsychotic therapeutic windows,^{43–45} and the serum antipsychotic level is correlated neither with therapeutic response nor with the side-effect of EPS.⁴⁶ The neuroleptic blood level has a hundred-fold variation among neuroleptic-medicated patients,⁴⁷ so that there is no reliable data to justify the cost for its routine monitoring.^{16,42}

The advent of non-neuroleptic atypical antipsychotics

After the introduction of clozapine by Sandoz Pharmaceuticals (East Hanover, New Jersey) in 1990 on the market, American psychiatry entered into a new era of antipsychotic psychopharmacology. The last antipsychotic (loxapine) before clozapine, was approved by the US Food and Drug Administration (FDA) in 1975. Clozapine has been approved and indicated for neuroleptic treatment-refractory schizophrenic patients in treating both positive and negative symptoms. It is also accepted that clozapine is more effective than other typical antipsychotic agents.^{15,48} Before starting on clozapine, the patient needs to meet four requirements:⁴⁸ (1) the patient has schizophrenia; (2) the patient is older than 16 years; (3) at least three other neuroleptics have been ineffective or the patient developed side-effects of tardive dyskinesia; and (4) white blood cells (WBC) counts are done weekly by the Clozaril (Clozapine) Patient Management System (CPMS) by Caremark, a contracted managed care company in collaboration with Roche Laboratories (Nutley, New Jersey).⁴⁹ Yielding to the pressure of the concern over the cost (\$9,000 a year for both medication and WBC monitoring), the manufacturer “unbundled” the CPMS in 1992. Since then the patient has been able to get a weekly supply of clozapine with a satisfactory WBC count which can be done in any laboratory of the patient’s or the physician’s choice. The unbundled clozapine annual cost is still \$4,200 for the medication alone. Hopefully, the cost of clozapine would be further reduced by price competition — an important

American market practice after the FDA approves more new atypical antipsychotics. Beside clozapine, Janssen Pharmaceutical’s (Titusville, New Jersey) risperidone has been available since February 1994. Both Canadian and American multicenter research data suggested that 6 mg/day of risperidone is the optimal dose for maximal efficacy and minimal induction of the EPS. At 6 mg daily, risperidone was effective against both positive and negative symptoms and was superior to haloperidol in managing chronic schizophrenia.^{50,51} Now, several more antipsychotic agents have been filed or are in the process of filing at the FDA.²⁹

Due to the risk of developing agranulocytosis^{48,52} and the cost of clozapine, American psychiatrists pay special attention to the manufacturer’s instructions for indication for use and the drug administration procedure.⁴⁷ As recent as June 1994, 52 months after its FDA release of clozapine on the market, two clinical case reports describing two 14 year-old clozapine-treated adolescents (boy and girl) were published in a national official Academy journal.^{53,54} According to Physician’s Desk Reference (PDR),⁴⁸ clozapine is started with 25 mg/day and moved up slowly with the daily increment of 25 mg up to 300 mg/day. The clozapine treatment for the elderly is recommended with 12.5 mg/day as the starting dose with the increment of 6.25 or 12.5 mg every three days.⁵⁵ In any case, the patient needs to be monitored for WBC weekly.

Risperidol does not have the risk of the fatal side-effect of agranulocytosis,^{50,51} and costs only half of what clozapine does. American psychiatrists are starting to feel more comfortable with the use of risperidone rather than clozapine. It is also been found effective for improving both the positive and negative symptoms of schizophrenia. However, its efficacy for neuroleptic treatment-refractory schizophrenia needs to be proven.

Management of a antipsychotic-induced side-effects

There are clinical research data^{17,56} to link the neuroleptic doses and the severity of acute EPS, which consists mainly of dystonia, akathisia, and Parkinsonian symptoms (muscle rigidity, bradykinesia, and tremors). If left untreated, the EPS can be an ongoing source of the patient’s distress and can affect his/her compliance with antipsychotic therapy.⁵⁷ Based on the concept of neuronal feedback loop hypothesis of DA nigrostriatal symptoms,⁵⁸ the clinician adds an anticholinergic agent, or a DA agonist (e.g. amantadine), or a benzodiazepine to re-establish the new neurotransmission circuit equilibrium in this feedback loop to alleviate the EPS.^{57,59} Anticholinergic agents are not usually prescribed as a prophylaxis for the EPS,⁵⁹ although a recent report reviewing nine studies indicates their value to prevent dystonia with concomitant use of anticholinergic agents.⁶⁰

An anticholinergic agent is the mainstay of treatment for the EPS, but its use needs periodically to be assessed, reassessed, and discontinued if no longer indicated.⁵⁹ There are no reliable treatments for tardive dyskinesia.⁶¹ A recent report of using vitamin E (α -tocopherol) at the dosage level of 1600 IU/day to treat tardive dyskinesia seems to be promising.⁶²

Most antipsychotics (especially low-potency neuroleptics and clozapine) lower the seizure threshold. Yet, the use of antipsychotics for patients with a history of seizures is usually not contraindicated. Clozapine-medicated patients have an overall rate of 2.8% seizures which are dose-related (1% in less than 300 mg/day, 2.7% in 300–600 mg/day, and 4.4% in 600–900 mg/day range).^{48,63} Seizures associated with clozapine treatment occurred at a crude rate of 3.5% in a state hospital.⁶⁴ Valproic acid, but not carbamazepine, is recommended to be the medication of choice as an anticonvulsant to control this adverse effect.^{29,49}

Sedation is commonly associated with initial antipsychotic use especially for those who are taking low-potency neuroleptics and clozapine. Using a dosing technique of gradual increments, most patients can tolerate the antipsychotic without experiencing further sedation. Sometimes in the course of treatment, the choice of using a less sedating high-potency neuroleptic is necessary.

Antipsychotics interfere with brain thermoregulation.⁵ The patients receiving antipsychotics do not tolerate extreme ambient temperature well.^{5,65} Neuroleptic malignant syndrome^{66,67} is rare but attracts attention because of its morbidity and mortality. The treatments for this syndrome are supportive therapy, the withdrawal of the offending antipsychotic agent, and the use of dantrolene, bromocriptine, amantadine, or electroconvulsive therapy.⁶⁶

Low-potency neuroleptics and clozapine produce anticholinergic adverse effects, such as blurred vision, dryness of the mouth, constipation, urinary retention, or mental confusion. About one-third of clozapine-medicated patients experience hypersalivation, which can be tolerated and disappears later on in the course of treatment. Some patients need an anticholinergic agent to control excessive salivation.²⁹

Low-potency neuroleptics and clozapine have α -adrenergic blocking effects which cause orthostatic hypotension. The patients usually tolerate this side-effect and need to be advised to rise from bed gradually. Cardiac arrhythmias with increased QT interval or polymorphic ventricular tachycardia (*torsade de pointes*) are also reported with their neuroleptic use.

Rarely, patients with antipsychotic therapy also experience dermatologic side effects (skin lesions and photosensitivity), eye changes (mainly from chlorpromazine and thioridazine), endocrine effects (sexual dys-

function,^{10,11} gynecomastia, and weight gain), and hepatic side-effects (jaundice, elevated liver enzymes).

Agranulocytosis has been implicated very rarely with chlorpromazine⁴⁸ and with clozapine (1–2%).⁶⁸ Clozapine-induced agranulocytosis is potentially fatal. Recently, filgrastim, a granulocyte colony-stimulating factor has been used to shorten the duration of agranulocytosis induced by clozapine.^{69,70}

The Characteristics of Antipsychotic Prescribing in the US

Every culture has its own characteristics of psychiatric practice including the pharmacotherapy of schizophrenia.

Usually, the American psychiatrists prescribe one antipsychotic medication at a time. The Japanese and French psychiatrists tend to prescribe two or more antipsychotics concurrently.^{71,72} The total sum of daily chlorpromazine equivalent dosage levels from different antipsychotics for a Japanese patient could be higher than that from a single agent for an American patient.⁷¹

The practice of using an “energizing” or “activating” phenothiazine (such as trifluoperazine) in the morning and using another “sedating” phenothiazine (such as chlorpromazine) at night, has been out of fashion since late 1970’s. In the US, the polypharmacy of prescribing two or more antipsychotics at a time is considered undesirable. Adjunctive medications (such as antiparkinsonian agents, benzodiazepines, etc.) for the neuroleptic-medicated patients need to be assessed carefully for their indications of the concomitant use with an antipsychotic.⁷³

American patients receive intramuscular depot neuroleptic injections less frequently than their European counterparts. It is estimated that only 10–20% of neuroleptic-medicated schizophrenic patients receive depot antipsychotics in the US while as many as 50% of their British counterparts have intramuscular injection with long-acting medications.⁷⁴ Currently, the available depot neuroleptics in America are fluphenazine decanoate (25 mg/ml) and haloperidol decanoate (50 mg/ml). Fluphenazine was first approved in 1963 in enanthate form, which was shortly replaced with the decanoate form. Haloperidol decanoate was introduced in the US in 1986.⁷⁴ The following might be reasons for this underutilization for depot injection: (1) There is a cultural preference for oral medication in the US; (2) only 2 of the 9 existing depot neuroleptics are available in America whereas 5 forms are accessible to British patients.⁷⁵ Both available American long-acting injectable neuroleptics are high-potency in nature and tend to produce more EPS than the other seven depot agents; (3) the patient’s right to refuse depot injection is honored in the US; and (4) some American psychiatrists have misconceptions about the increased risk of the depot neuroleptic-induced major side-effects.⁷⁴ A recent literature review does not

support the belief that there is more risk of neuroleptic malignant syndrome, tardive dyskinesia, and the EPS with depot forms compared to oral neuroleptic forms.⁷⁴

There are 13 chemically different antipsychotic agents on the US market (see Table 1). Nine of those 13 American medications are available in Japan, a country where there are about 26 total available kinds of antipsychotic medications. Some of them were developed by Japanese pharmaceutical companies. The total number of available Japanese antipsychotics agents is closer to that of available agents in European countries. As of 1989, there were 39 agents marketed around the world.⁷⁶

In the US the psychiatrists give patients prescriptions which are filled at any pharmacy of the patient's or the insurance company's choice. Unlike Japanese physicians, American physicians usually do not dispense medications from their own clinics. American psychiatrists spend more time per clinic visit with their outpatients. But the total frequency of clinic visits per patient within a year is less in America than in Japan. The patients in the US can have their prescriptions refilled directly by their own pharmacists usually on a monthly basis without the need of making clinic visits with their psychiatrists if they continue enjoying a good remission state. The 60 outpatients that a Japanese psychiatrist may see daily⁷⁷ is unheard of in the US even by a psychiatrist of a "high medication" practice group.⁷⁸

American psychiatrists are under much more legal pressure than any foreign psychiatrists because more than two-thirds of the attorneys on earth are practicing in the US. As a result, American psychiatrists worry much more about the side-effect of tardive dyskinesia from neuroleptics than its incidence would warrant.⁷⁹ Partly due to legal concerns, medical records (especially inpatient notes) are excessive. Foreign-born doctors from Asia, Europe and Africa are often impressed with the volume of American paper work and computer output. At the same time, the people from accreditation bodies naively believe and equate the quality of medical care to both the quantity of paper work and the careful write-up of the so-called "treatment plan." Within this kind of lego-medical and bureaucratic environment, the decision to start an antipsychotic, is usually well-justified and documented although the indication for its use is looser among institutionalized elderly or mentally retarded patients.

For inpatient care, the average length of hospitalization for treating patients with most diseases is shorter in America (9.1 days in 1990) than in Japan (50.5 days in 1989),⁸⁰ partly due to the pressure of cost containment being placed on American doctors. For schizophrenic patients, the average hospital stay was 632 days in Japan in 1989⁸¹ while the average hospital stay was 12 days in America in the same year.⁸² The reasons to explain the lengthy inpatient stay in Japan are the civil commitment

laws permitting long-term involuntary hospitalization,⁷¹ the stigma of the mental illness which discourages many Japanese families from accepting patients back into the home,⁷¹ and the lack of community alternatives to hospitalization.^{71,83} Furthermore, the parental value of *amae* (meaning over-protection or spoiling) in the Japanese culture⁸⁴ discourages families from placing a schizophrenic youngster elsewhere. The family usually does not like to accept the patient home directly from the hospital until after he/she has achieved a remission with more normalized socio-occupational adjustment.

Closing Remarks

As indicated previously, this review is intended only to familiarize Japanese readers with the American scene of antipsychotic prescribing. It is not intended as a comprehensive review dealing with pharmacologic treatment strategy for schizophrenia or other psychotic disorders. Therefore, many important related topics are omitted. My partial list of these omitted pharmacotherapy-related topics are treatment issues in comorbidity (substance abuse with alcohol⁸⁵ and cocaine as well as depression⁸⁶), the concomitant use of mood-stabilizing agents (lithium, carbamazepine, valproic acid, etc.), electroconvulsive therapy, the concurrent use of benzodiazepines or other adjunctive medications,⁷³ drug interactions,⁸⁷ treatment refractoriness, treatment non-compliance, and psychoeducation about pharmacotherapy.⁸⁸

Since the heady early days of the 1950's, neuroleptic medications have become old hat, and the thrill has worn off.⁷⁹ But the recent introduction of atypical antipsychotics such as clozapine and risperidone has excited American psychiatry in search of better antipsychotic agents. The simplest definition for atypical antipsychotics is that they are not likely to cause catalepsy in laboratory animals and have a wide therapeutic ratio for their antipsychotic effects and EPS side-effects.⁸⁹ From a clinical standpoint, the atypicality of antipsychotic agents would be defined by the low propensity to produce acute EPS and tardive dyskinesia relative to typical drugs like haloperidol and chlorpromazine.⁸⁹

The imperfect dopamine hypothesis of schizophrenia has been again under intensive revision to understand how typical and atypical antipsychotic agents work. Table 2 is a brief list of biochemical characteristics of the atypical antipsychotics (clozapine and risperidone).^{15,29,48,49,89–97} There is currently more knowledge of neurotransmission profiles,⁹⁸ and better understanding of D₁:D₂ dopamine receptor interactions.⁹⁹ The researchers in the near future are expected to discover more "designer" antipsychotic agents which not only give better antischizophrenic efficacy but are reasonably devoid of undesirable side-effects. The possible innovative atypical antipsychotic candidates fall roughly into five groups: The late substi-

Table 2 The Characteristics of Atypical Antipsychotics (Clozapine and Risperidone)

Acting selectively on mesolimbic/cortical DA systems ^{15,50,51}
Acting less preferentially on nigrostriatal DA system ^{15,50,51,90}
^a Not acting on the tuberoinfundibular DA system ^{90,91}
^b Binding proportionately more DA D ₁ receptors ⁹²
^b Having a relatively lower affinity for DA D ₂ receptors ^{92,93}
^c Having more 5-HT ₂ blocking property ^{94,95}
Having greater ratio of 5-HT ₂ /D ₂ binding affinity ^{96,97}
Having non-significant sigma receptor blocking property ⁹⁷
^a Having more muscarinic cholinergic blocking property ⁹⁷

^a Not shown in risperidone; ^b Proven only in clozapine;^c Not from human data

tuted benzamides, the mixed DA and serotonin receptor antagonists, the DA specific compounds, serotonin receptor antagonists, and sigma receptor antagonists.¹⁰⁰ By then, the landscape of American antipsychotic prescribing will have a fresh new dimension.

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