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High doses or rapid dose escalation of aripiprazole may be more effective for treating schizophrenia

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A Japanese group reported that olanzapine (OLZ) and risperidone (RIS) were superior to aripiprazole (APZ) for treating newly admitted acute schizophrenia patients [1]. Treatment was initiated at APZ 12 mg/day. The mean dose was 23.6 mg/day, and the maximum dose of 30 mg/day was used in only 48% of cases. The rate of increase was not reported, but APZ treatment was discontinued within two weeks in 35% of patients and within four weeks in 50% of patients. Other reports have shown that APZ is as effective as OLZ and RIS and has fewer side effects than OLZ or RIS [2][3]. The Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness has recommended both APZ and RIS as first-line antipsychotics [4].

At the emergency unit of the Okayama Psychiatric Medical Center, in 2008, we admitted 70 drug-naïve acute schizophrenia patients newly diagnosed according to the DSM-4. We prescribed APZ to six of these patients, and it was effective in five to 30 days (Table 1). We initiated APZ treatment at 12 mg/day and increased the dose to 24–30 mg/day in two to 16 days. None of the six patients exhibited adverse reactions. One patient was not responsive to APZ, RIS, OLZ, or quetiapine. By contrast, the use of RIS resulted in three cases of malignant syndrome among 51 patients.

We also prescribed APZ for a drug-naive 25-year-old female schizophrenia out-patient. We initiated treatment at APZ 3 mg/day and increased the dose to 12 mg/day over three months, but she did not improve and we therefore discontinued treatment. After three months, she became delusional, and violent toward her daughter as a result. We then initiated treatment at APZ 30 mg/day. After one month, her symptoms had improved, and after six months we reduced her dose to a maintenance dose of APZ 12 mg/day.

Another patient, a 38-year-old female, exhibited improvement in her positive symptoms at OLZ 20 mg/day, but we switched her to APZ because she felt sedated and couldn't do housework. We added 24 mg/day of APZ, and then gradually reduced her OLZ dose to nothing. Now, she takes only 12 mg/day of APZ and can do housework.

One possible reason for the difference may be that Japanese psychiatrists start APZ treatment at the lowest dose and then increase the dose slowly, and this may not allow the true efficacy of APZ to be achieved. This has become the customary practice in Japan because of the Japanese government's emphasis on safety. The middle dose of APZ (15 mg/day) has been reported to induce akathisia more than the higher doses (20 mg and 30 mg/day) [5]. Aripiprazole has a relatively long half-life of about 60 hours, and the time required to achieve the steady-state concentration (almost 2 weeks) may therefore be another reason for initiating APZ treatment at a higher dose and then increasing the dose rapidly to avoid delayed onset of

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efficacy. Occupancy of 90% of the dopamine D2 receptors is needed to ameliorate the symptoms of schizophrenia, and 30 mg/day of APZ is required for efficient D2 occupancy at this level [6]. The delay in the onset of APZ efficacy may be reduced by high doses or rapid dose escalation of APZ.

Table 1. Six Patients With Drug-Naive Acute Schizophrenia

Age /sex	D.U.P.	Type	Day 1	Maximum dose	CGI-I	PANSS (day 1 → 28)	Adjuvant
53/F	5 months	paranoid	12 mg	30 mg (after 14 days)	1	101→33	
50/M	1 year	paranoid	12 mg	24 mg (after 16 days)	2	101→68	VPA 800 mg
28/M	1.5 years	paranoid	12 mg	30 mg (after 12 days)	1	105→34	
18/M	2 years	hebephrenic	12 mg	30 mg (after 8 days)	5	113→109	
35/M	9 years	hebephrenic	12 mg	30 mg (after 2 days)	3	114→71	VPA 1000 mg
50/F	10 months	paranoid	12 mg	24 mg (after 4 days)	1	107→35	VPA 800 mg

D.U.P.: duration of untreated psychosis; CGI-I: Clinical Global Impressions-Improvement
PANSS: Positive and Negative Syndrome Scale; VPA: valproic acid

REFERENCES

[1] Hatta K, Sato K, Hamakawa H, Takebayashi H, Kimura N, Ochi S, Sudo Y, Asukai N, Nakamura H, Usui C, Kawabata T, Hirata T, Sawa Y. Effectiveness of second-generation antipsychotics with acute-phase schizophrenia. Schizophr Res 2009; 113: 49-55.

[2] McQuade RD, Stock E, Marcus R, Jody D, Gharbia NA, Vanveggel S, Archibald D, Carson WH. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. J Clin Psychiatry 2004; 65: Suppl 18, 47-56.

[3] Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, Stringfellow J, Ingenito G, Marder SR. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs. placebo in patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 2003; 60: 681-690.

[4] Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, Docherty JP. Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry 2009; 70 Suppl 4, 1-46.

[5] Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, Saha A, Ali M, Iwamoto T., 2003. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res 2003; 61: 123-136.

[6] Gründer G, Fellows C, Janouschek H, Veselinovic T, Boy C, Bröcheler A, Kirschbaum KM, Hellmann S, Spreckelmeyer KM, Hiemke C, Rösch F, Schaefer WM, Vernaleken I. Brain and plasma pharmacokinetics of aripiprazole in patients with schizophrenia: an [18F]fallypride PET study. Am J Psychiatry 2008; 165: 988-995.