図2

統合失調症と抗精神病薬の関係

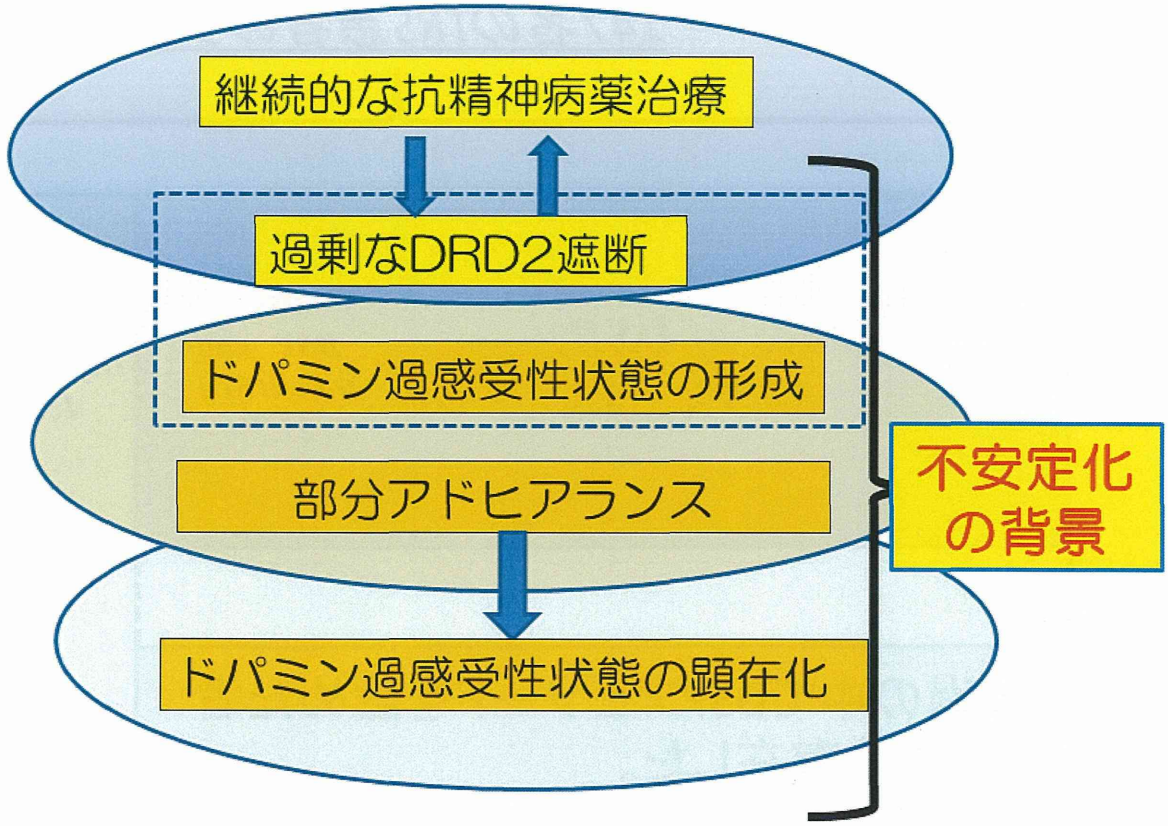


図3　千葉・山形県3施設の治療抵抗性統合失調症患者

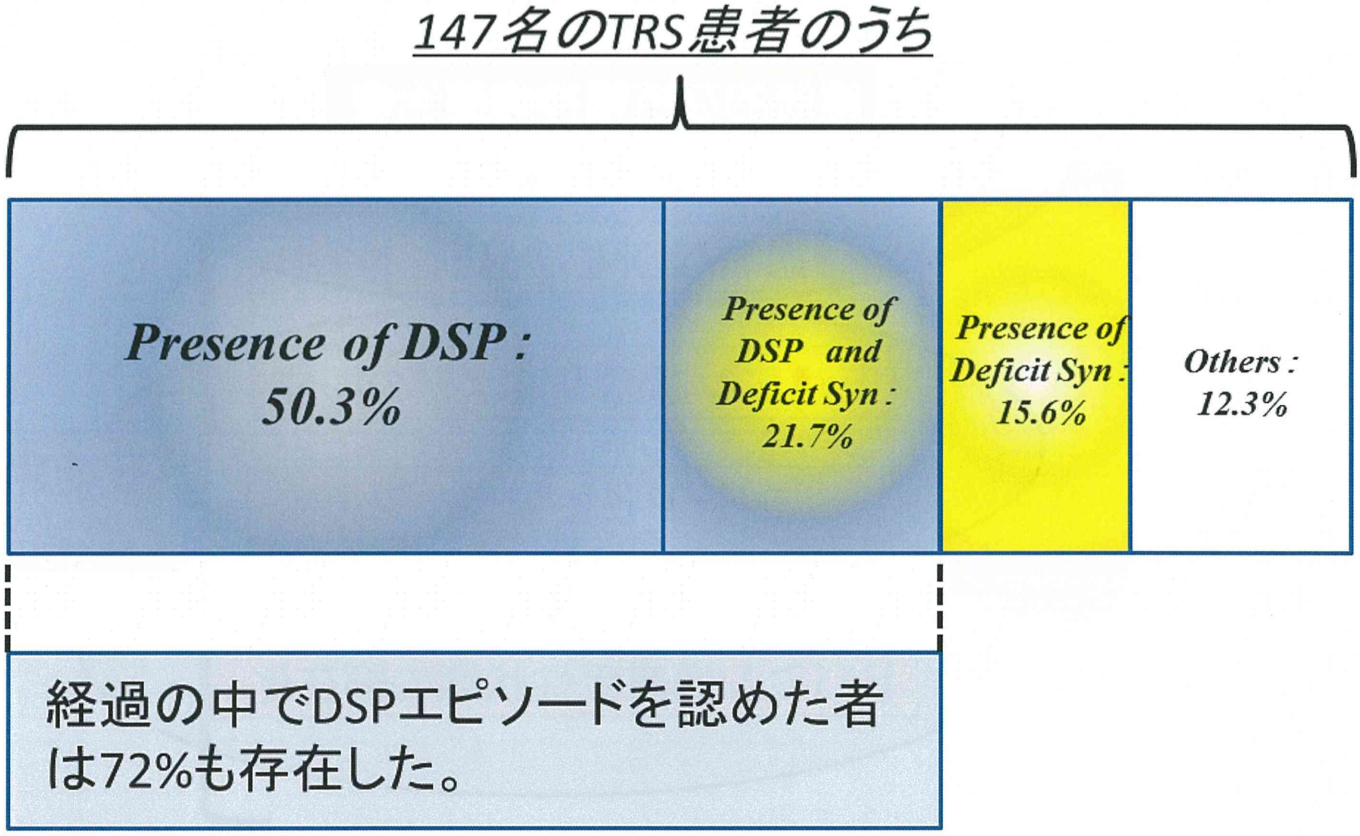


図4

ARI切り替え後の転帰

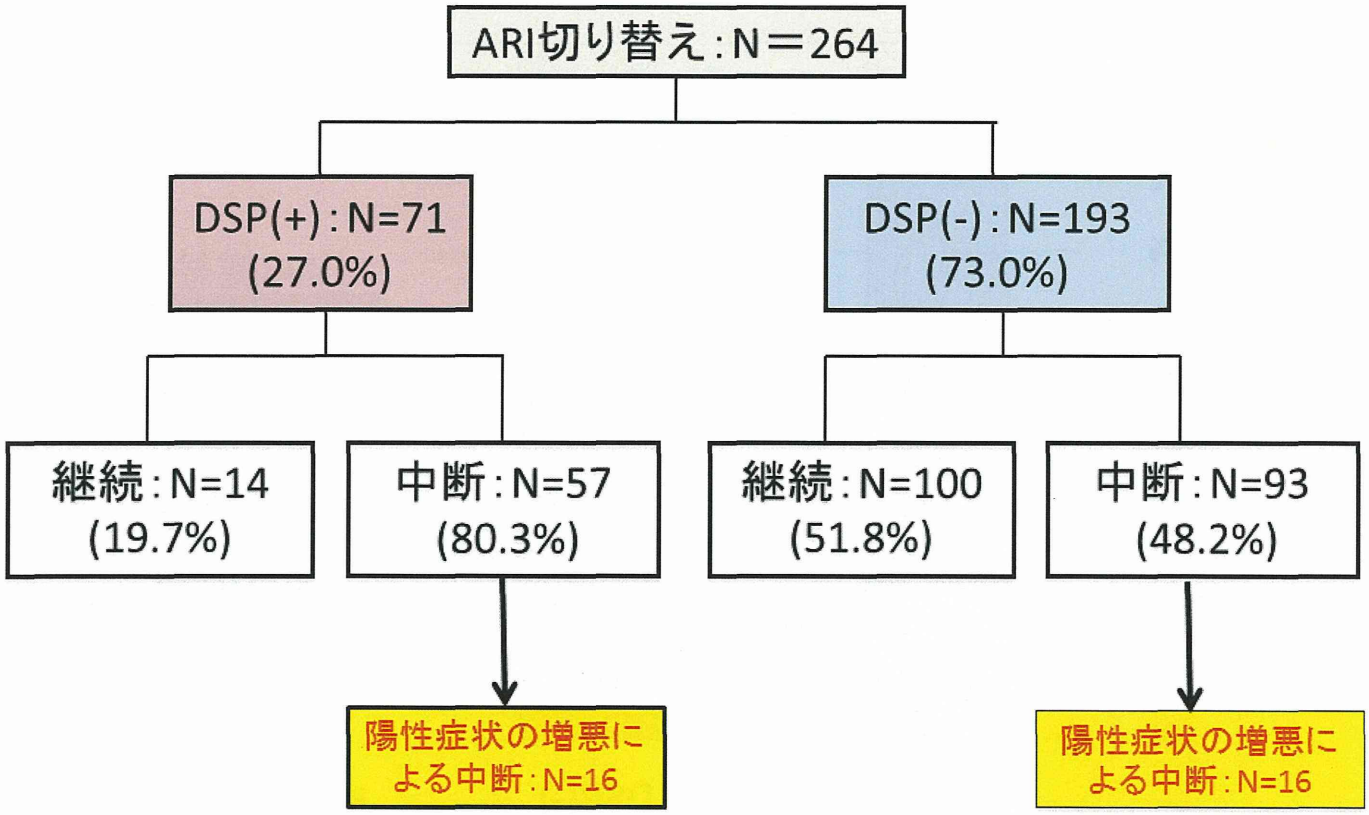


図5

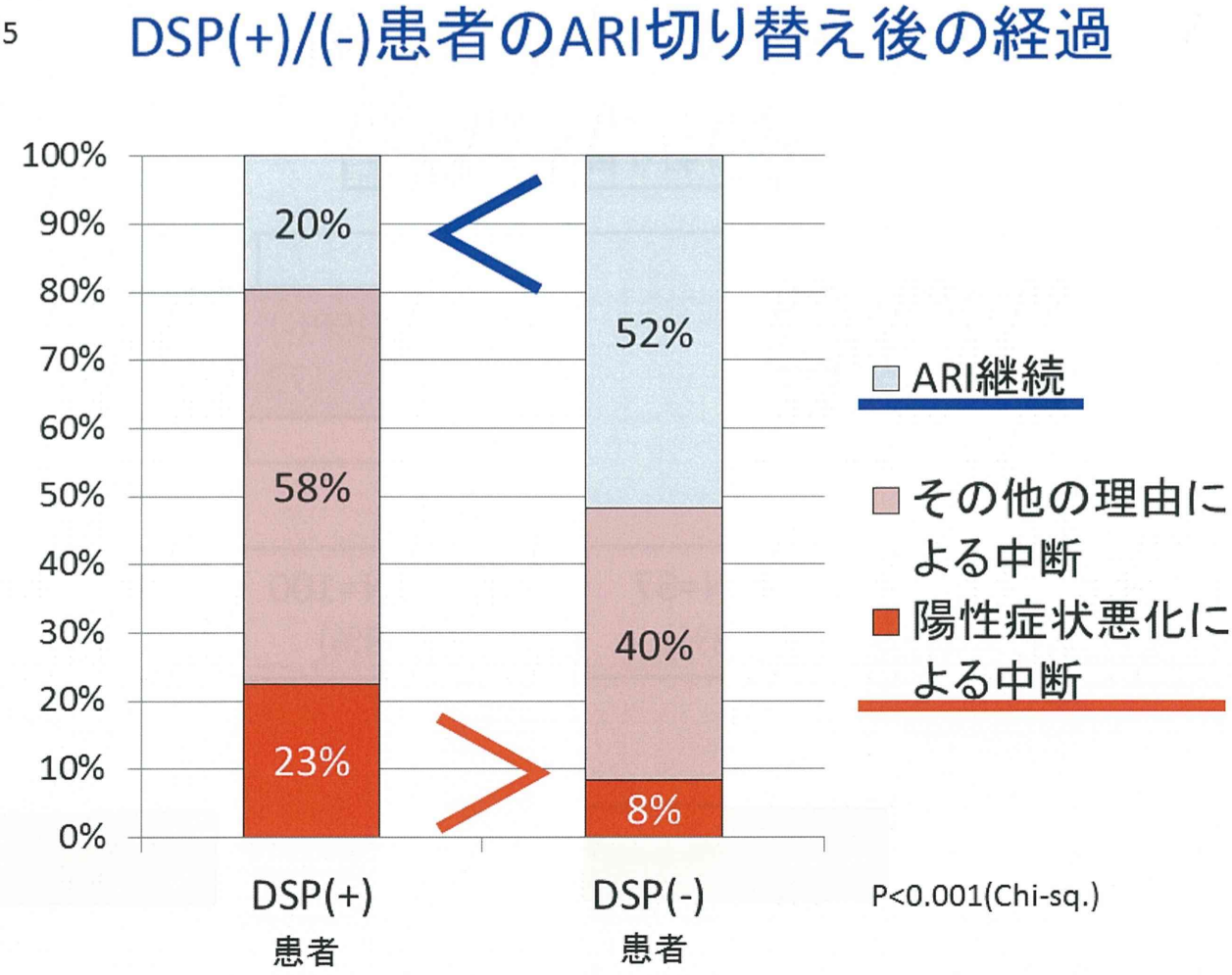

DSP(+)/(-)患者のARI切り替え後の経過
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
20%
58%
23%
52%
40%
8%
ARI継続
その他の理由による中断
陽性症状悪化による中断
DSP(+)
患者
DSP(-)
患者
P<0.001(Chi-sq.)

図6

前治療薬の平均用量（CP換算）

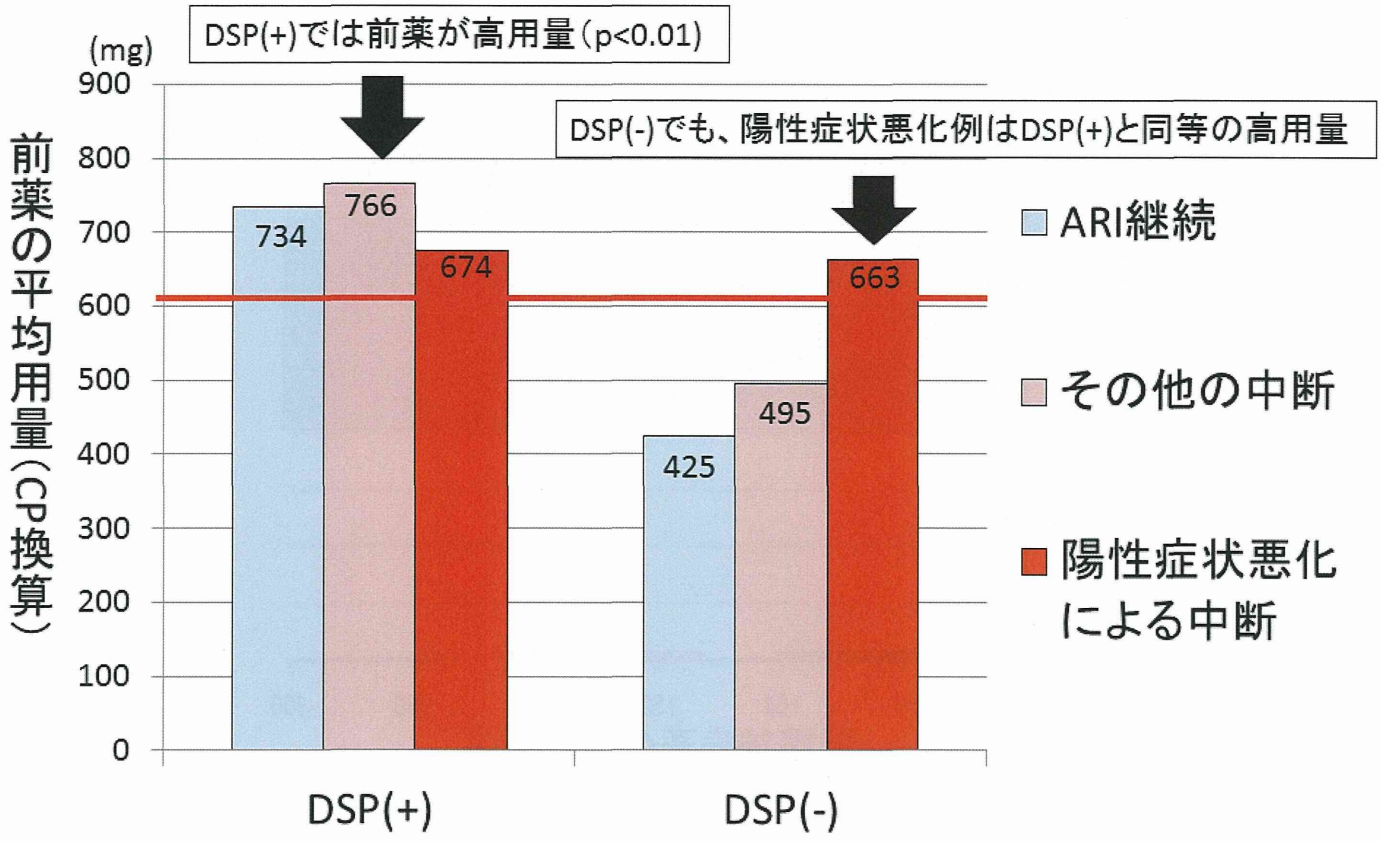
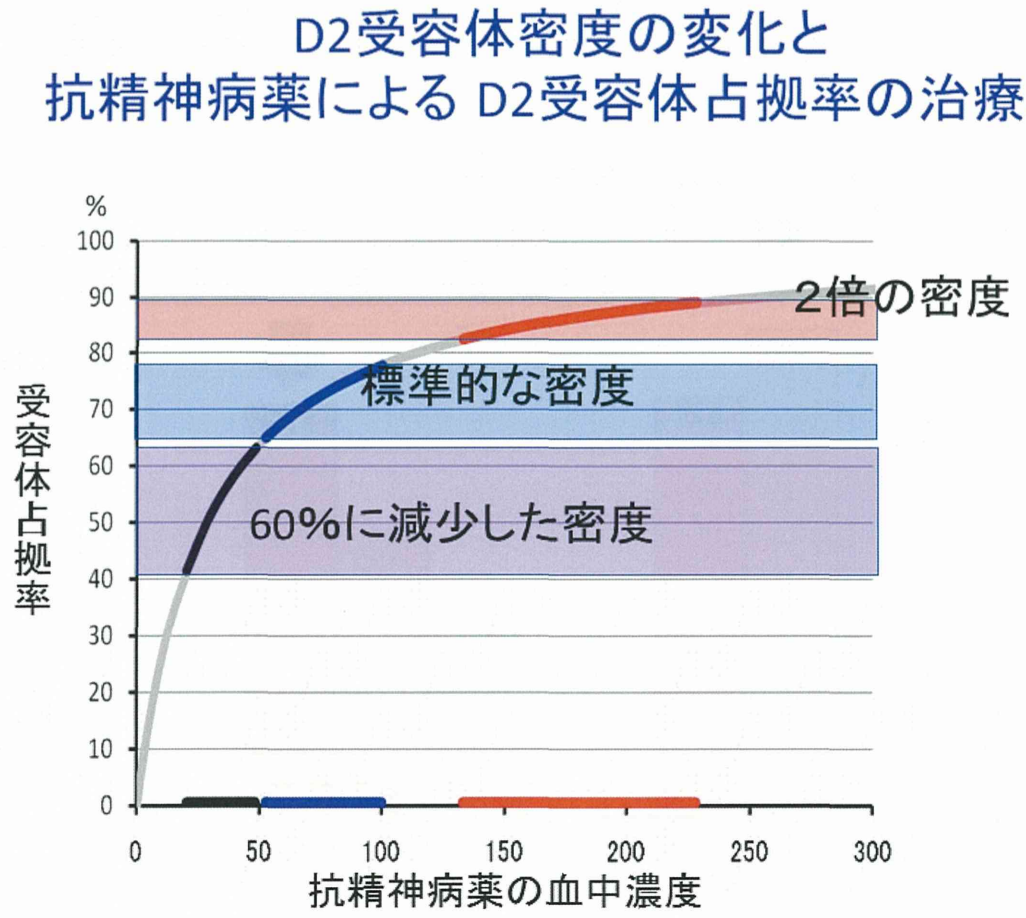


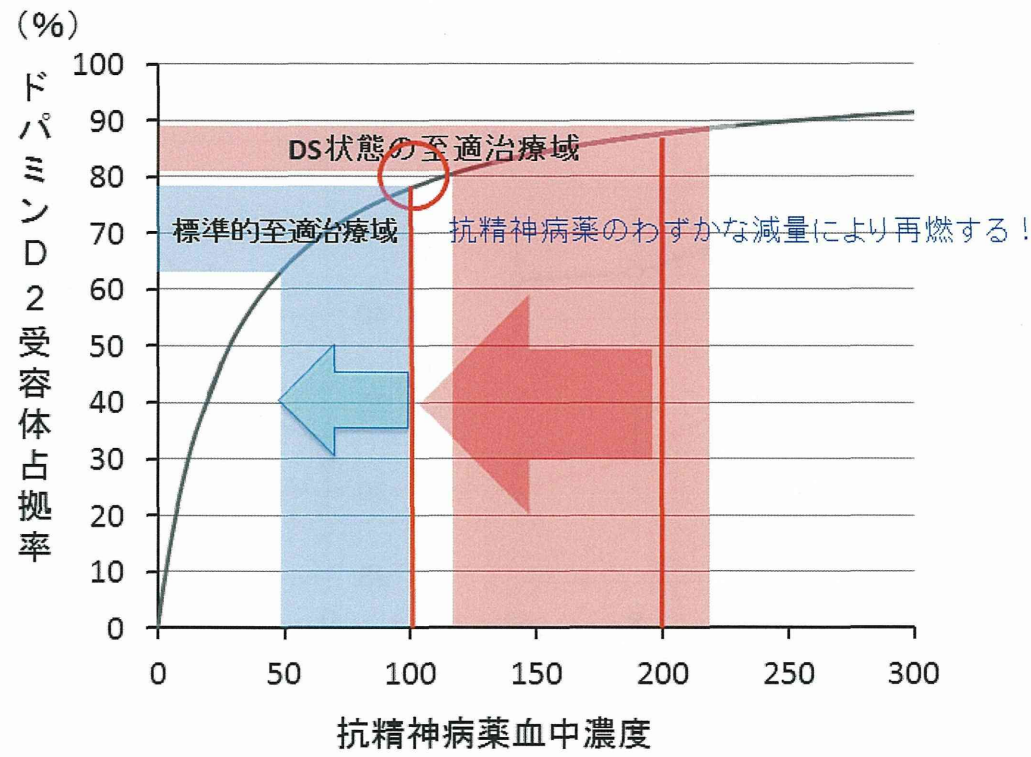
図7



Iyo et al., 2013

図8

1消失半減期における抗精神病薬の体内からの消失量
標準的状態とドパミン過感受性(DS)状態の違い



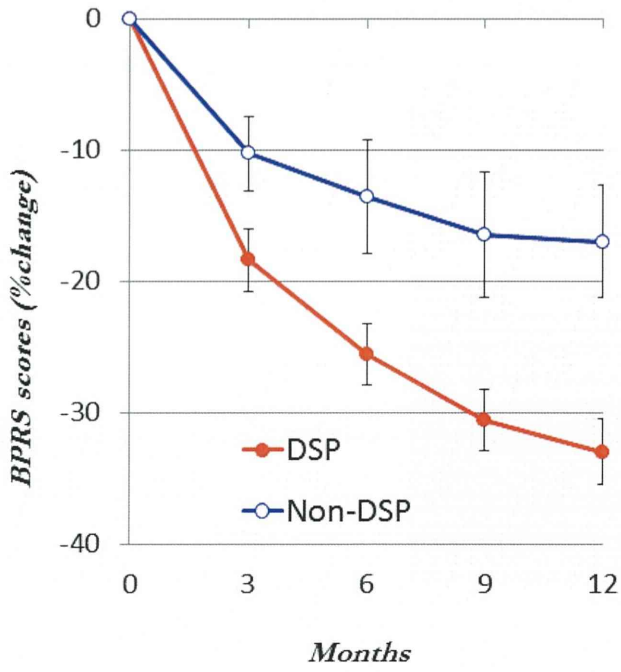
Iyoら, 2013

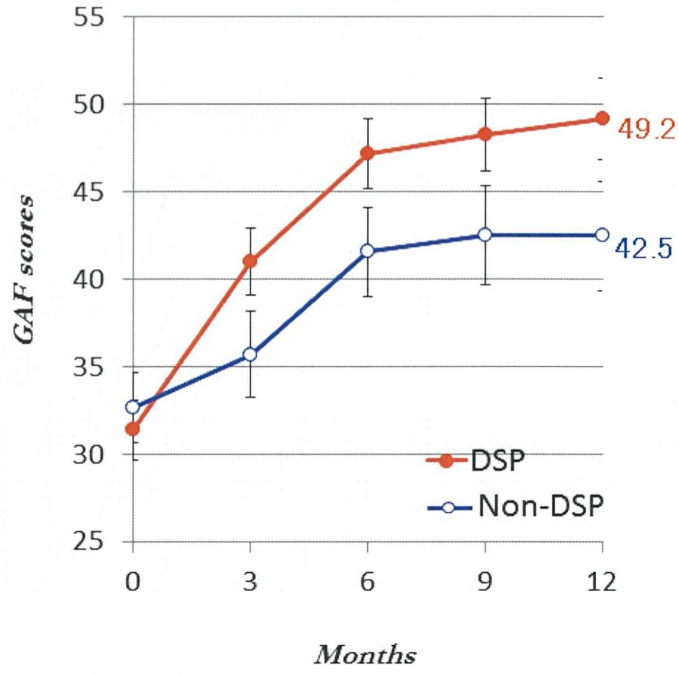
図9

CREST試験の結果

Number of Subjects

DSP group	62	60	56	54	52
NonDSP group	33	31	26	24	23

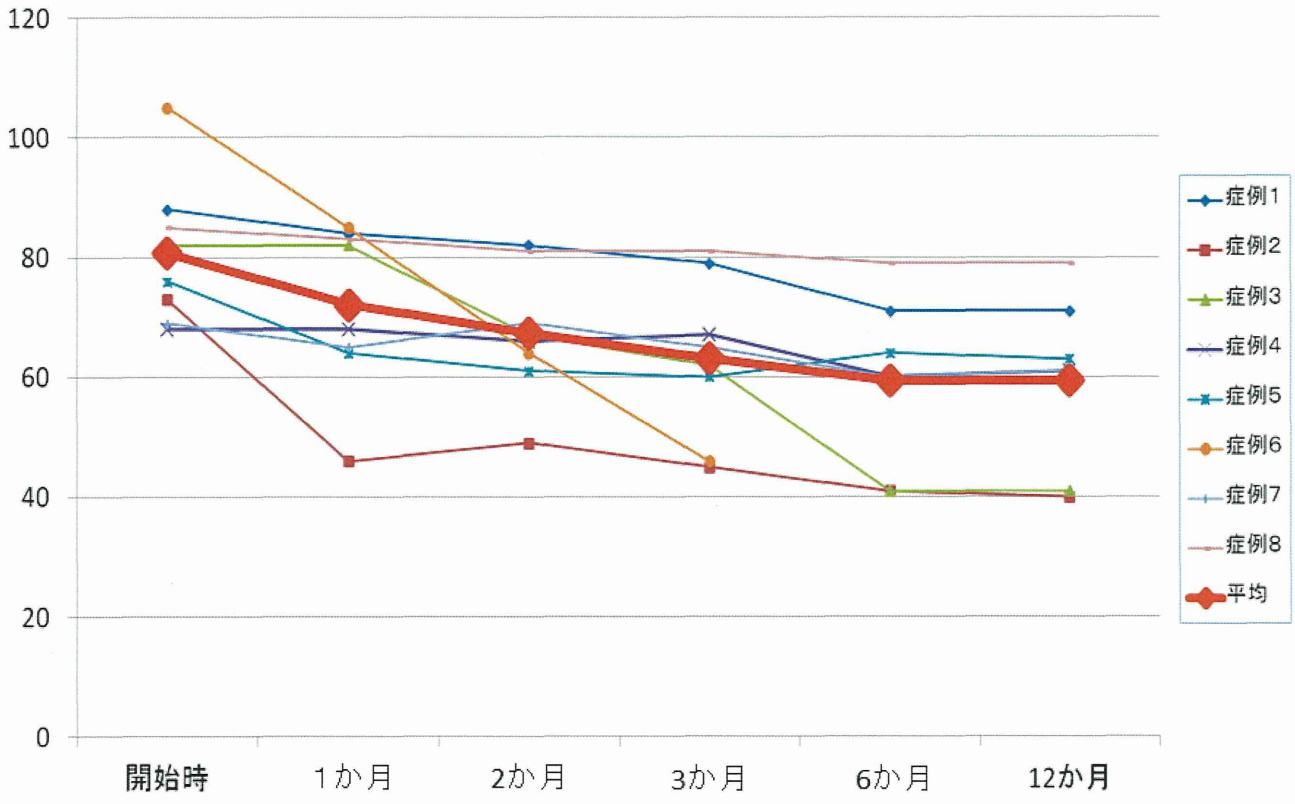




Kimura et al., Schizophr Res 2014

図10

BNS追加・薬剤整理によるBPRS推移



研究成果の刊行に関する一覧表

（平成 24～26 年度）

研究成果の刊行に関する一覧表（平成24年度～平成26年度）

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
伊豫雅臣	過感受性精神病治療抵抗性統合失調症の治療・予防法の追求	伊豫雅臣 中込和幸	過感受性精神病治療抵抗性統合失調症の治療・予防法の追求	星和書店	東京	2013	総ページ92頁

雑誌（英文）

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sasaki T, Hashimoto T, Niitsu T, Kanahara N, Iyo M.	Treatment of refractorycatatonic sc hizophrenia with low dose aripiprazole.	An n. Gen. Psychiatry	11(1)	12	2012
Iyo M, Tadokoro S, Kanahara N, Hashimoto T,Niitsu T, Watanabe H, Kashimoto K.	Optimal extent of dopamine D2 receptor occupancyby antipsychotics for treatment of dopamine supersensitivity psychosis and late-onset psychosis.	J. Clin. Psychopharmacol.	33	398-404	2013
Kanahara N, Sekine Y, Haraguchi T, Uchida Y, Hashimoto K, ShimizuE, Iyo M.	Orbitofrontal cortex abnormality and deficit schizophrenia.	SchizophreniaResearch	143 (2-3)	246-252	2013
Kimura H, Kanahara N, Watanabe H, Iyo M.	Potential treatment strategy of risperidone in long-acting injectable form for schizophrenia with dopamine supersensitivity psychosis.	Schizophrenia Research	145	130-131	2013
Takase M, Kanahara N, Oda Y, Kimura H, Watanabe H, Iyo M.	Dopamine supersensitivity psychosis and dopamine partial agonist: A retrospective survey of failure of switching to aripiprazole in schizophrenia.	J. Psychopharmacol			2015

Kimura H, Kanahara N, Komatsu N, Ishige M, Muneoka K, Yoshimura M, Yamanaka H, Suzuki T, Komatsu H, Sasaki T, Hashimoto T, Hasegawa T, Shiina A, Ishikawa M, Sekine Y, Shiraishi T, Watanabe H, Shimizu E, Hashimoto K, Iyo M	A prospective comparative study of risperidone long-acting injectable for treatment-resistant schizophrenia with dopamine supersensitivity psychosis.	Schizophr. Research	155	52-58	2014
Komatsu H, Sekine Y, Okamura N, Kanahara N, Okita K, Matsubara S, Hirata T, Komiyama T, Watanabe H, Minabe Y, Iyo M.	Effectiveness of information technology aided relapse prevention programme in schizophrenia excluding the effect of user adherence: a randomized controlled trial.	Schizophr. Research	150	240-244	2013
Kanahara N, Yoshida T, Oda Y, Yamanaka H, Moriyama T, Hayashi H, Shibuya T, Nagaushi Y, Sawa T, Sekine Y, Shimizu E, Asano M, Iyo M.	Onset pattern and long-term prognosis in schizophrenia: 10-year longitudinal follow-up study.	PLoS One	8(6)	e67273	2013

雑誌（和文）

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
宮澤惇宏，榎原雅代，金原信久，藤崎美久，伊豫雅臣	Clozapine によって頻回の解離症状・自傷行為が消失した治療抵抗性統合失調症の１例.	臨床精神薬理	15(9)	1551-1557	2012
渡邉博幸	多職種チームで取り組む地域精神医療の再構築―組織行動学的視点から組織変革をこころみる－	. 文化看護学会誌	4	66-76	2012
渡邉博幸	「抱える」医療から「つなぐ」医療へ-総合病院精神科のダウンサイジングと地域精神医療の取り組み-	日本社会精神医学会雑誌	21	116-123	2012
渡邉博幸，吉野智，高野則之，色川大輔，長谷川信也，青木勉	千葉県東部における精神保健の取り組み－精神科多職種アウトリーチと中核地域生活支援センターとの連携－	精神科臨床サービス	12	216-220	2012
渡邉博幸	地域における効果のみられたチーム医療.	統合失調症.	3	90-100	2012
渡邉博幸	統合失調症における抑うつ症状の薬物治療.	精神科治療学	28	19-22	2012

鈴木智崇	強迫症状と伴う統合失調症	精神科治療学	28	23-27	2012
金原信久，渡邉博幸，伊豫雅臣	疫学的知見からみた急性精神病へのアプローチ	精神科治療学	28	29-34	2012
金原信久，木村大，山中浩嗣，渡邉博幸，伊豫雅臣	ドパミン D2 受容体過感受性からみた治療抵抗性統合失調症の理解と治療戦略	臨床精神薬理.	17 (12)	1617-1623	2014
髙瀬正幸，金原信久，伊豫雅臣.	非定型抗精神病薬持効性注射剤の可能性：アドヒアランス維持とドパミン過感受性精神病の予防・改善.	臨床精神薬理	17	635-641	2014
金原信久，鈴木智崇，伊豫雅臣	Clozapine のより具体的な適応症例：治療抵抗性統合失調症の評価に際して	臨床精神薬理	17(2)	261-275	2014
金原信久，宗岡克政，木村大，伊豫雅臣	非定型持効性注射剤による統合失調症難治例への取り組み	精神科治療学	29(1)	37-44	2014

研究成果の刊行物・別刷

Sasaki et al. Annals of General Psychiatry 2012, 11:12
http://www.annals-general-psychiatry.com/content/11/1/12

ANNALS OF GENERAL PSYCHIATRY

CASE REPORT Open Access

Treatment of refractory catatonic schizophrenia with low dose aripiprazole

Tsuyoshi Sasaki[1,2*], Tasuku Hashimoto[2], Tomihisa Niitsu[3], Nobuhisa Kanahara[2] and Masaomi Iyo[1,2]

Abstract

This case is of 54-year-old female with catatonic schizophrenia, characterized by treatment resistance to the pharmacotherapy with olanzapine, risperidone, flunitrazepam, and ECT. Olanzapine and risperidone and flunitrazepam did not improve her catatonic and psychotic symptoms, and induced the extrapyramidal symptoms. The effects of ECT did not continue even for a month. However, the treatment with low-dose aripiprazole dramatically improved the patient's psychotic symptoms and extrapyramidal symptoms. The mechanisms underlying the effects of low-dose aripiprazole in this case remain unclear, but unlike other antipsychotics, aripiprazole is a dopamine D2 partial agonist. In this regard, our results suggest that aripiprazole has numerous advantages, especially in cases of stuporous catatonia and a defective general status.

Background

Catatonia, which is characterized by motoric immobility such as catalepsy or stupor, mutism, negativism, is shown in about 10-15% of patients with schizophrenia [1]. Published works to date demonstrate variable treatment with benzodiazepines, electroconvulsive therapy (ECT), N-Methyl-D-Asparte (NMDA) antagonists, and antipsychotics, even the atypical, which remain discussed, because of worsening in symptomatology and increasing the risk of inducing neuroleptic malignant symdrome [2-4]. Aripiprazole, a dopamine D2 receptor partial agonist, is different from other atypical antipsychotics, which are common profile of D2 receptor antagonist.

We present a patient of catatonic schizophrenia, which was markedly improved on low-dose aripiprazole, after failing to respond to olanzapine, risperidone, and ECT.

Case presentation

A 54-year-old woman began to experience auditory hallucinations, including a voice admonishing her to deny herself, and delusions of persecution and reference, and to withdraw socially. She gradually entered a catatonic stupor with insomnia and anorexia. Her mother took her to a mental clinic, where she was diagnosed with catatonic-type schizophrenia. She was prescribed risperidone 1 mg/day and flunitrazepam 1 mg/day for approximately 4 months, but her withdrawal and stupor state did not improve, and she was referred to another hospital at 55 years of age. No abnormalities were found in her general laboratory examinations or brain CT. She reported having consistent pathological experiences, such as hallucination and delusions, and her diagnosis was confirmed as catatonic-type schizophrenia according to the DSM-IVcriteria. We discontinued her previous medications and prescribed olanzapine 20 mg/day and flunitrazepam 1 mg/day for approximately 2 weeks. However, her catatonic stupor with anorexia and severe extrapyramidal symptoms was not improved. She was referred to a general hospital, and began to receive electroconvulsive therapy (ECT). The ECT treatment was enforced twice for six weeks per week (total 12 times). The treatment with ECT and risperidone 3 mg/day and flunitrazepam 2 mg/day almost completely eliminated her psychotic symptoms, and she was again able to take meals by herself, but a high level of extrapyramidal symptoms remained. She was transferred to our hospital. After another month of ECT, however, she began to experience auditory hallucinations, and delusions of persecution and reference, along with stupor with insomnia and anorexia again. We changed her drug regimen from risperidone and flunitrazepam to only aripiprazole 3 mg/day. Two weeks later, her catatonic stupor and psychotic symptoms were dramatically improved without extrapyramidal symptoms. She was again able to take meals alone and was able to go

* Correspondence: sasaki@faculty.chiba-u.jp
[1]Department of Child Psychiatry, Chiba University Hospital, Inohana 1-8-1, Chiba, 260-8670, Japan
[2]Department of Psychiatry, Chiba University Graduate School of Medicine, Inohana 1-8-1, Chiba, 260-8670, Japan
Full list of author information is available at the end of the article

shopping with her mother. She is now 59 years old and has been treated with only 3 mg/day aripiprazole for 48 months. She has no recrudescence of psychotic symptoms or extrapyramidal symptoms, and continues to help her mother with the housework.

Discussion

This case is of 54-year-old female with catatonic schizophrenia, characterized by treatment resistance to the pharmacotherapy with olanzapine and risperidone and flunitrazepam, and ECT. To our knowledge, this is the first published report to show that the treatment-resistant schizophrenic patient with the catatonic subtype was improved, using ultra-low-dose aripiprazole. In this case, olanzapine and risperidone and flunitrazepam did not improve her catatonic and psychotic symptoms, and induced the extrapyramidal symptoms. The effects of ECT did not continue even for a month. However, the treatment with low-dose aripiprazole dramatically improved the patient's psychotic symptoms and extrapyramidal symptoms. Although it has been reported that atypical antipsychotics and benzodiazepines were effective for stuporous catatonia [5], olanzapine and risperidone ,and flunitrazepam did not improve the psychotic symptoms of our patient; moreover, they exacerbated her extrapyramidal symptoms. Although benzodiazepines, such as lorazepam, are the first choice for the catatonic features as well as ECT [5], and their high-doses are frequently used, benzodiazepines might cause respiratory arrest. So we were not able to used for it. The mechanisms underlying the effects of low-dose aripiprazole in this case remain unclear. Recently Vörös et al and Kirino reported that aripiprazole is effective for catatonic stupor [6,7]. Also it has been reported that ECT-aripiprazole combination therapy has an excellent safety profile and therapeutic efficacy [8,9]. The present case responded to ECT but began to relapse one month after the course of ECT. So without the effects of ECT, it would be uncertain whether aripiprazole alone could have resolved her long-term stupor state. In this regard, our results suggest that aripiprazole might have advantages, especially in cases of stuporous catatonia and a defective general status like the present case.

Conclusion

We reported here a case of successful treatment using low-dose aripiprazole monotherapy for a female patient after the ECT in cases of stuporous catatonia and a defective general status.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TS, TH, TN and NK wrote the manuscript. MI is the principal investigator of this study. All authors read and approved the final manuscript.

Acknowledgements

The authors thank Tadashi Hasegawa (Chiba University) for his advice.

Author details

[1]Department of Child Psychiatry, Chiba University Hospital, Inohana 1-8-1, Chiba, 260-8670, Japan. [2]Department of Psychiatry, Chiba University Graduate School of Medicine, Inohana 1-8-1, Chiba, 260-8670, Japan. [3]Research Center for Child Mental Development, Chiba University Graduate School of Medicine, Inohana 1-8-1, Chiba, 260-8670, Japan.

Received: 23 February 2012 Accepted: 12 April 2012
Published: 3 May 2012

References

1. Taylor MA, Fink M: Catatonia in psychiatric classification: a home of its own. *Am J Psychiatry* 2003 Jul, 160(7):1233–1241.
2. Penland HR, Weder N, Tampi RR: The catatonic dilemma expanded. *Ann Gen Psychiatry* 2006 Sep 7, 5:14.
3. Carroll BT, Goforth HW, Thomas C, Ahuja N, McDaniel WW, Kraus MF, Spiegel DR, Franco KN, Pozuelo L, Muñoz C: Review of adjunctive glutamate antagonist therapy in the treatment of catatonic syndromes. *J Neuropsychiatry Clin Neurosci* 2007, 19(4):406–412.
4. Rosebush PI, Mazurek MF: Catatonia and its treatment. *Schizophr Bull* 2010, 36(2):239–242. Epub 2009 Dec 7.
5. Van Den Eede F, Van Hecke J, Van Dalfsen A, Van den Bossche B, Cosyns P, Sabbe BG: The use of atypical antipsychotics in the treatment of catatonia. *Eur Psychiatry* 2005 Aug, 20(5–6):422–429.
6. Vörös V, Tényi T: Use of aripiprazole in the treatment of catatonia. *Neuropsychopharmacol Hung* 2010 Jun, 12(2):373–376.
7. Kirino E: Prolonged catatonic stupor successfully treated with aripiprazole in an adolescent male with schizophrenia: a case report. *Clin Schizophr Relat Psychoses* 2010, 4(3):185–188.
8. Lopez-Garcia P, Chiclana C, Gonzalez R: Combined use of ECT with aripiprazole. *World J Biol Psychiatry* 2009, 10(4 Pt 3):942–943.
9. Masdrakis VG, Oulis P, Zervas IM, Karakatsanis NA, Kouzoupis AV, Karapoulios E, Soldatos CR, Masdrakis VG: The safety of the electroconvulsive therapy-aripiprazole combination: four case reports. *J ECT* 2008, 24(3):236–238.

doi:10.1186/1744-859X-11-12
Cite this article as: Sasaki *et al.*: Treatment of refractory catatonic schizophrenia with low dose aripiprazole. *Annals of General Psychiatry* 2012 11:12.

Optimal Extent of Dopamine D2 Receptor Occupancy by Antipsychotics for Treatment of Dopamine Supersensitivity Psychosis and Late-Onset Psychosis

Masaomi Iyo, MD, PhD,† Shigenori Tadokoro, MD,* Nobuhisa Kanahara, MD, PhD,* Tasuku Hashimoto, MD, PhD,* Tomihisa Niitsu, MD, PhD,‡ Hiroyuki Watanabe, MD, PhD,* and Kenji Hashimoto, PhD†*

Abstract: Several studies have proposed an optimal dopamine D2 receptor occupancy by antipsychotics (OOc) to establish optimal pharmacological treatment of schizophrenia. However, there are limitations to the use of the OOc, especially in application to patients with treatment-resistant schizophrenia, including dopamine supersensitivity psychosis (DSP) or late-onset psychosis (LOP). It has been suggested that D2 receptor density is up-regulated by chronic treatment of antipsychotics in DSP, whereas it may be low in LOP owing to age-related reduction. In estimation of the proposed OOc, these alterations have not been taken into account, which may be one of the factors contributing to the limited application of this index. We here hypothesize that there is an optimal range in the number of D2 receptors available for dopamine binding to elicit adequate neurotransmission in the treatment of patients with schizophrenia. We then estimated the OOc under the assumption that the range is constant while D2 density is variable. The results showed that the OOc and plasma level of antipsychotics increase with an increase in the D2 density but decrease with a decrease in the D2 density. That is, if the range of OOc is 65% to 78% in a standard D2 density, it becomes 82% to 89% under 2-fold up-regulated density and 42% to 63% under a 40% reduced density. The results also indicated that the reduction of the plasma antipsychotic level is greater during a given time period in patients with higher D2 density, as they need a higher antipsychotic dose to achieve the raised OOc, which would account for the clinical features of DSP, for example, acute exacerbation after a discontinuation of antipsychotics. On the other hand, in patients with lower D2 density, only a lower antipsychotic dose will achieve the OOc, and a small increase in the dose will result in a greater increase in occupancy and induce extrapyramidal adverse effects more easily. Furthermore, the reduction of the plasma antipsychotic level during the time period is smaller, which prolongs extrapyramidal adverse effects after discontinuation of antipsychotics in LOP. We also attempted to develop a strategy for the prevention and treatment of patients with DSP or LOP by focusing on D2 density.

Key Words: schizophrenia, dopamine supersensitivity, late-onset psychosis, antipsychotics, dopamine D2 receptors, occupancy

(*J Clin Psychopharmacol* 2013;33: 398–404)

Schizophrenia is a disabling mental illness with a lifetime prevalence of 0.4% to 1.0% worldwide,[1] and the course of illness is usually chronic with relapses despite treatment.[2] For decades, the standard treatment protocol has included the administration of D2 dopamine receptor blockers as effective antipsychotics, especially for the amelioration of psychotic symptoms.[3,4] Evidence-based or expert consensus guidelines for the dosing of various antipsychotics have been published to improve the quality of care of patients with schizophrenia.[5] However, it has been reported that a substantial percentage of patients receive daily antipsychotic doses greater than the recommended range[6] and that such overly high doses of antipsychotics, while not always ideal, are often clinically justifiable.[7]

To establish an optimal treatment strategy to achieve the highest rate of response with the lowest incidence of adverse effects of antipsychotics, an optimal plasma level of antipsychotics has been explored.[8] At the same time, the D2 receptor occupancy of antipsychotics estimated by using positron emission tomography (PET) and single-photon emission computed tomography has provided more direct information on the relationships between the effects of antipsychotics and their sites of action, that is, D2 receptors, in the living human brain.[9] Such imaging indicates that there is an optimal D2 receptor occupancy of antipsychotics (OOc).[9] However, there are limitations to the use of either the optimal plasma level or OOc,[10] especially in application to patients with treatment-resistant schizophrenia.[11,12]

D2 RECEPTOR DENSITY AND TREATMENT-RESISTANT SCHIZOPHRENIA

It has been estimated that more than half of treatment-resistant schizophrenia cases may be related to dopamine supersensitivity psychosis (DSP),[13] and the proposed features of DSP are shown in Table 1. Dopamine supersensitivity psychosis, which was initially a problem in the 1970s, has recently been on the rise again, possibly as a result of patients switching their antipsychotic therapy from first-generation antipsychotics (FGAs) to second-generation antipsychotics (SGAs).[13,14] One of the mechanisms underlying DSP is suggested to be up-regulation of dopamine D2 receptor density, as the density of these receptors has been shown to increase by at least 2-fold after long-term treatment with antipsychotics,[15] a finding that agrees with postmortem studies.[16] In experimental animals as well, chronic or subchronic treatment of D2 receptor antagonists increases D2 receptor density,[17–19] and induces behavioral supersensitivity.[19] Taken together, these results suggest that one of the mechanisms underlying DSP is up-regulation of D2 receptor density after long-term treatment of antipsychotics, although there has also been a study suggesting that no up-regulation occurs.[20] The treatment difficulty in patients with DSP may therefore be due to increased density of D2 receptors.

From the *Department of Psychiatry, Graduate School of Medicine, †Division of Clinical Neuroscience, Center for Forensic Mental Health, and ‡Research Center for Child Mental Development, Graduate School of Medicine, Chiba University, Chiba, Japan.
Received September 28, 2011; accepted after revision October 9, 2012.
Reprints: Masaomi Iyo, MD, PhD, 1-8-1 Inohana, Chiba 260-8670, Japan (e-mail: iyom@faculty.chiba-u.jp).

ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e31828ea95c

TABLE 1. Proposed Features of DSP

Feature	
Tolerance development for antipsychotics	Development of tolerance for antipsychotics occurs in patients with DSP and leads to an increase in doses needed for control of psychotic symptoms
Tardive dyskinesia as a predictor	Presence or history of tardive dyskinesia is often observed in patients with DSP and is the best predictor of DSP
Acute relapse or exacerbation of psychosis	Acute relapse or exacerbation of psychosis appears after dose reduction or discontinuation of antipsychotics
Vulnerability to minor stress	Even minor life events and psychosocial stress induce relapse or exacerbation of psychotic symptoms

On the other hand, approximately 10% of all cases of first-episode schizophrenia occur in individuals older than 45 years, that is, they are cases of late-onset psychosis (LOP). These elderly patients sometimes show therapeutic effects at lower doses of antipsychotic medication than younger patients, but there is a general tendency for greater susceptibility to extrapyramidal side effects (EPS) and tardive dyskinesia (TD) in these patients.[21] Because the D2 receptor density in the human brain decreases with age[22–24] at a rate of approximately 10% per decade,[24] this age-related reduction may be associated with the difficulty in treatment of these individuals, suggesting an etiology opposite that in treatment-resistant DSP.

Taken together, these findings suggest that alteration in D2 density may play important roles in the treatment resistance of patients with DSP or LOP, in the inappropriateness of the reported OOc for these patients, and in the discrepancy in antipsychotic doses between the evidence-based recommendations in guidelines and real clinical settings. Therefore, we here consider the OOc and plasma level of antipsychotics from the viewpoints of ligand-receptor interaction and estimation of the D2 receptor occupancy, although there may be other factors influencing treatment difficulty in these patients, such as differences in the pharmacokinetics of antipsychotics, including gene-based or age-related differences.

OPTIMAL D2 RECEPTOR OCCUPANCY AND PLASMA LEVEL OF ANTIPSYCHOTICS, AND D2 RECEPTOR DENSITY

Number of D2 Receptor-Dopamine Complexes and Response to Dopamine

It is known that dopamine exhibits its activity by binding to D2 receptors in a dose-dependent manner.[25,26] On the other hand, the level of dopamine may determine the number of

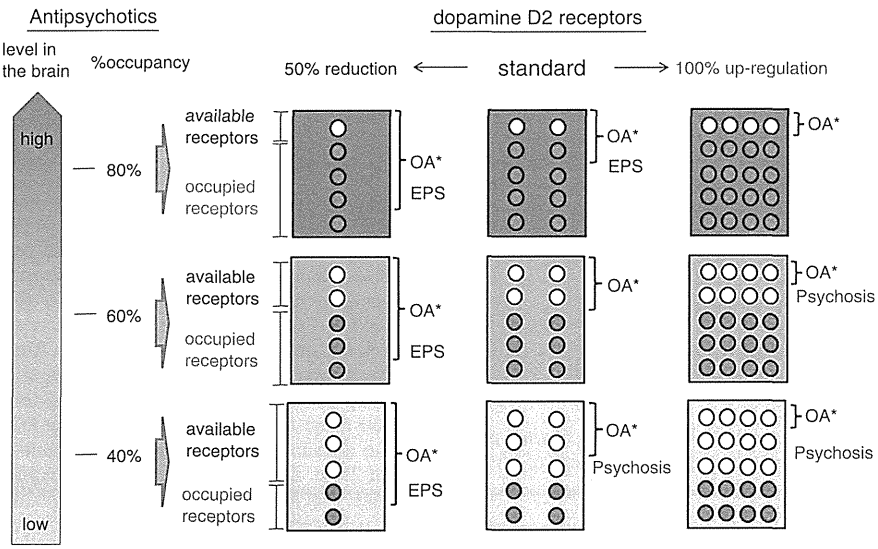


FIGURE 1. Relationships of brain levels and occupancy of antipsychotics to alterations in the D2 receptor density. We assumed 3 patterns of occupancy, that is, 40%, 60%, and 80%, under differently regulated conditions of D2 receptor density in this figure. We also assumed 10 receptors per unit under the standard condition, 20 receptors per unit under the 100% up-regulated condition, and 5 receptors per unit under the 50% down-regulated condition. We set 4 receptors as OA* in this case. Extrapyramidal side effect appears when the number of available receptors is lower than OA*, and psychosis appears when it is higher than OA*. OA* indicates the optimal number of available receptors, in this case. Open circles indicate available D2 receptors. Green circles indicate D2 receptors occupied by antipsychotics. One square indicates one unit volume as for D2 receptor density. Orange indicates levels of antipsychotic drugs, and darker orange means higher concentration of antipsychotic drugs.

D2 receptor-dopamine complexes under a constant level of D2 density, whereas the density of D2 receptors may determine the number of such complexes under a constant level of dopamine.[26] When antipsychotics occupy only a percentage of D2 receptors, the remainder of the D2 receptors may be available for dopamine binding and formulation of the D2 receptor-dopamine complexes; we refer to these as available D2 receptors (Fig. 1). Positron emission tomography studies suggest that there is an OOc for the treatment of patients with schizophrenia,[9,27] which suggests that there may be an optimal range in the number of available D2 receptors to yield adequate dopamine neurotransmission via D2 receptors in schizophrenia.

In experimental animals, it is known that chronic treatment of dopamine agonists compensatively decreases D2 density,[28] whereas chronic treatment of D2 receptor antagonists compensatively increases D2 density.[17–19] Our recent study indicated that a subchronic treatment with aripiprazole, a partial D2 receptor agonist, did not alter the D2 density in drug-naive rats, possibly because this treatment maintained adequate neurotransmission but reduced the D2 density that had been increased by a preceding subchronic treatment of haloperidol, a D2 full antagonist. These results suggest that an overblockade of dopamine transmission via D2 receptors compensatively increases D2 density, whereas an overstimulation decreases the density. On the other hand, adequate dopamine transmission maintains the density.

Considering these findings together, we hypothesize that compensatory changes in D2 density may occur to maintain a certain optimal range in the number of available D2 receptors that are necessary for adequate D2 receptor neurotransmission. We also propose that the optimal range of the number of available D2 receptors may be constant in the antipsychotic treatment of patients with schizophrenia, even when the D2 receptor density is varied.

Optimal Occupancy and Plasma Level of Antipsychotics, and Number of D2 Receptors

The ideal D2 receptor occupancy of antipsychotics (Oc) estimated by using PET is expressed as follows[27,29,30]:

$$Oc = [\,P/(P + ED50)] \tag{1}$$

where P is the plasma level of the antipsychotic drug and ED50 is the estimated plasma level of the antipsychotic drug associated with 50% receptor occupancy. Then, the OOc is expressed as follows:

$$OOc = [OP/(OP + ED50)] \tag{2}$$

where OP is the corresponding optimal plasma level.

Equations 1 and 2 indicate that the occupancy is determined by the plasma level and is independent of D2 receptor density. Therefore, the number of available D2 receptors may differ with the D2 receptor density even under the same occupancy. That is, as shown in Figure 1, even when the number of available D2 receptors is within the optimal range of available D2 receptors under the standard condition of D2 density, it may be lower under the down-regulated condition and higher under the up-regulated condition even under the same occupancy.

We calculated the OOc under the optimal number of available D2 receptors as a constant and the D2 receptor density as a variable. Here, the relationship between the ratio of the optimal number of available D2 receptors to the standard D2 density [ROA(s)] for an individual patient, and the OOc for standard D2 density [OOc(s)] is expressed as follows:

$$OOc(s) = 1 - ROA(s) \tag{3}$$

Then, ROA(s) becomes:

$$ROA(s) = 1 - OOc(s) \tag{4}$$

The ROA(s) may be known if OOc(s) is estimated by using PET or single-photon emission computed tomography.[9] Next, the optimal number of available D2 receptors, OA, is as follows:

$$OA = ROA(s) \times Rt(s), \tag{5}$$

where Rt(s) is the standard D2 receptor density. An OOc is then expressed as follows:

$$OOc = 1 - OA/Rt, \tag{6}$$

where Rt is the D2 receptor density. From equations 5 and 6, OOc becomes:

$$OOc = 1 - ROA(s) \times Rt(s)/Rt \tag{7}$$

Equation 7 indicates that the OOc is a dependent variable of Rt / Rt(s), where Rt / Rt(s) is the ratio of the D2 receptor density to the standard D2 receptor density. It is indicated that an increase in OOc occurs with an increase in D2 density, that is, up-regulation, whereas a decrease in OOc occurs with a decrease in the density. For example, if the range of the OOc is 65% to 78% under standard D2 density,[9] it increases to 82% to 89% under 2-fold up-regulated density, whereas it decreases to 42% to 63% under a 40% reduction in the D2 density (Fig. 2A).

Accordingly, Eq. 1 becomes:

$$OP = ED50/(1/OOC - 1) \tag{8}$$

Thereby, equations 6 and 8 yield:

$$OP = ED50 \times (Rt/OA - 1) \tag{9}$$

Therefore, higher doses of antipsychotic drug could be used for patients with higher D2 density. A dose increase in these patients would result in a higher plasma level[31] and thereby achieve the raised OOc. Here, when the plasma elimination half-life of the drug is the same, the plasma drug level decreases to a greater degree in cases of higher plasma level than in cases of lower plasma level during the same time period, for example, one plasma elimination half-life period (Fig. 2B). Therefore, the drug level dissociated from the receptors would be higher and the increase in the number of available D2 receptors would be greater in cases of higher plasma level during the same time period.

Equations 8 and 9 also indicate that the administration of lower doses of antipsychotic drug may achieve the OOc and that the corresponding optimal plasma level is lower in cases of lower D2 density (Fig. 2A). These potential associations in turn suggest that the level of drug elimination from the plasma would be smaller in cases of lower density than in cases of higher density during the same time period, when the elimination half-life is the same (Fig. 2C). Therefore, it would take a longer period to increase the number of available D2 receptors in cases of lower D2 density than in cases of higher D2 density.

When the width of OP and the width of the optimal range in number of available D2 receptors are OPw and OAw,

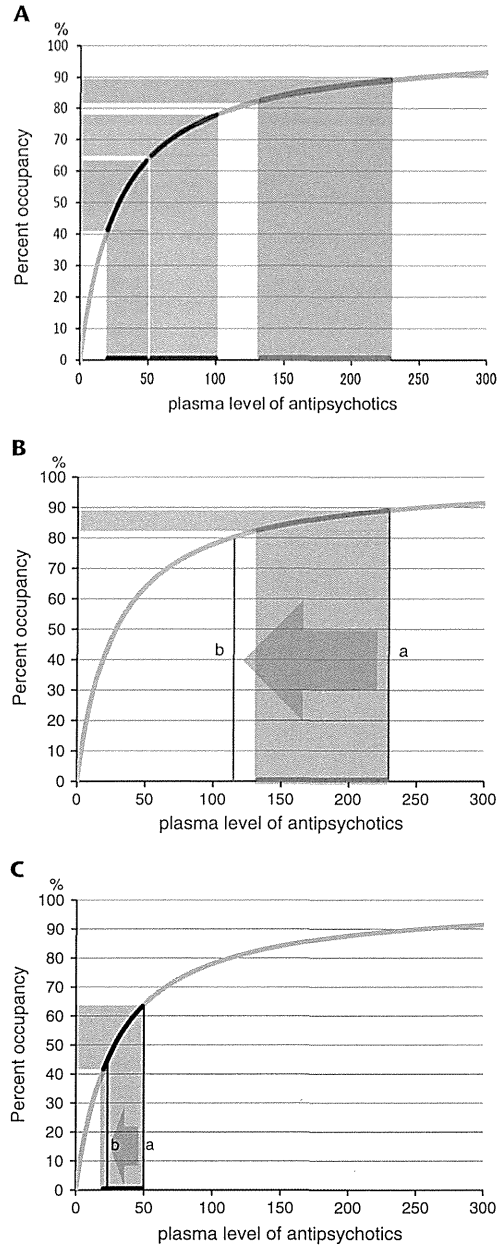


FIGURE 2. Assumed relationships between the optimal D2 receptor occupancy and plasma level of antipsychotics and the D2 receptor density. A, Relationship between the antipsychotic level and occupancy of D2 receptors. The range of the optimal D2 receptor occupancy of antipsychotics is shown under a standard condition of D2 density and in the 2-fold up-regulated and 40% reduced conditions. B, Reduction of D2 receptor occupancy and plasma level of antipsychotics during one plasma elimination half-life under an up-regulated condition of D2 density. Under a 2-fold up-regulated condition of D2 density, the plasma drug level and D2 occupancy level fall below the optimal range (b) even from the upper limit of the optimal level (a) during one elimination half-life of the drug. C, Reduction of D2 receptor occupancy and plasma level of antipsychotics during one plasma elimination half-life under a down-regulated condition of D2 density. Under a 40% reduced condition of D2 density, the plasma drug level and D2 occupancy level (b) is still within the optimal range from the upper limit of the optimal level (a) during one elimination half-life of the drug. The blue lines on the curve and *x*-axis, and the blue area indicate the optimal levels under the standard condition of D2 density; the red lines and red area indicate the optimal levels under the 2-fold up-regulated condition; and the black lines and purple area indicate the optimal levels under a 40% reduced condition. Red vertical lines indicate the duration of one plasma elimination half-life under a 2-fold up-regulated condition. Black vertical lines indicate the duration of one plasma elimination half-life under a 40% reduced condition.