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Figure Legends

Fig.1: Relationships of plasma levels and occupancy of antipsychotics to alterations in the D2 receptor density

To help clarify the relationships of the plasma levels and occupancy of antipsychotics to alterations in the D2 receptor density, we assumed 3 patterns of occupancy, i.e., 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. EPS 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.

EPS stands for extrapyramidal side effects.

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 color indicates levels of antipsychotic drugs and deeper orange color means higher concentration of antipsychotic drugs.

Fig.2: Assumed relationships between the optimal D2 receptor occupancy and plasma level of antipsychotics and the D2 receptor density

Fig.2A: 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 two-fold up-regulated and 40% reduced conditions.

Fig.2B: 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 two-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.

Fig.2C: 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.

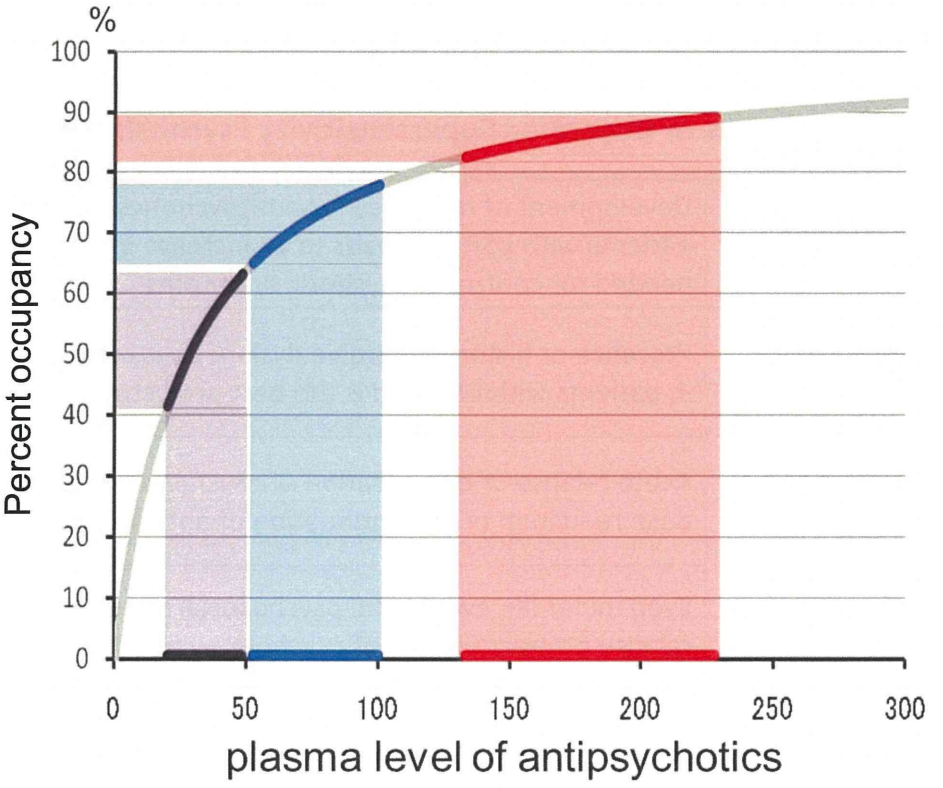
The blue lines on the curve and x-axis, and the blue area indicate the optimal levels under the standard condition of D2 density, the red lines and red area indicate the optimal levels under the two-fold up-regulated condition, and the black lines and purple area indicate the optimal levels under a 40% reduced condition.

Red vertical lines indicate the duration of one plasma elimination half-life under a two-fold up-regulated condition.

Black vertical lines indicate the duration of one plasma elimination half-life under a 40% reduced condition.

Proposed Features of Dopamine Supersensitivity Psychosis (DSP)	
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

Fig.2A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plasma level of antipsychotics

Fig.2B

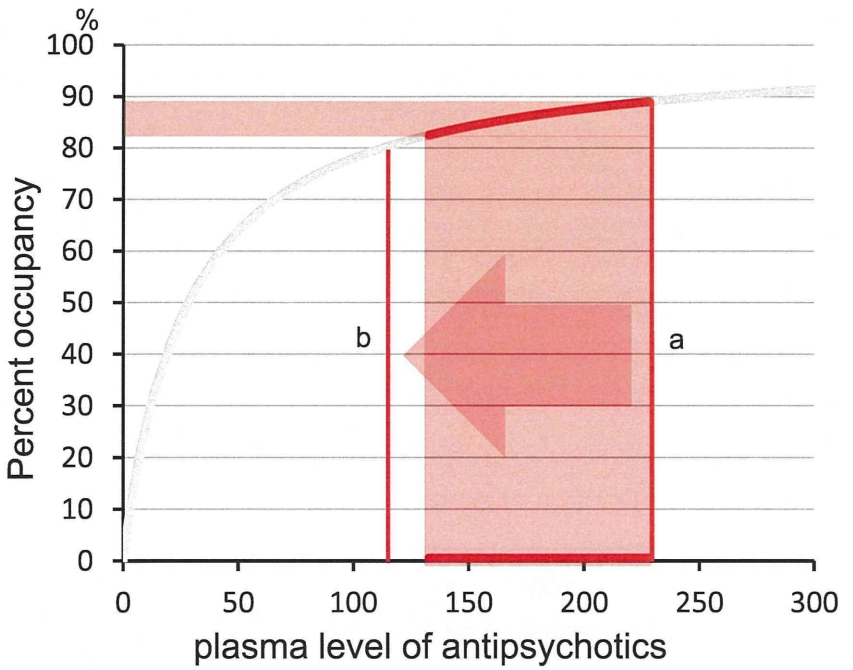
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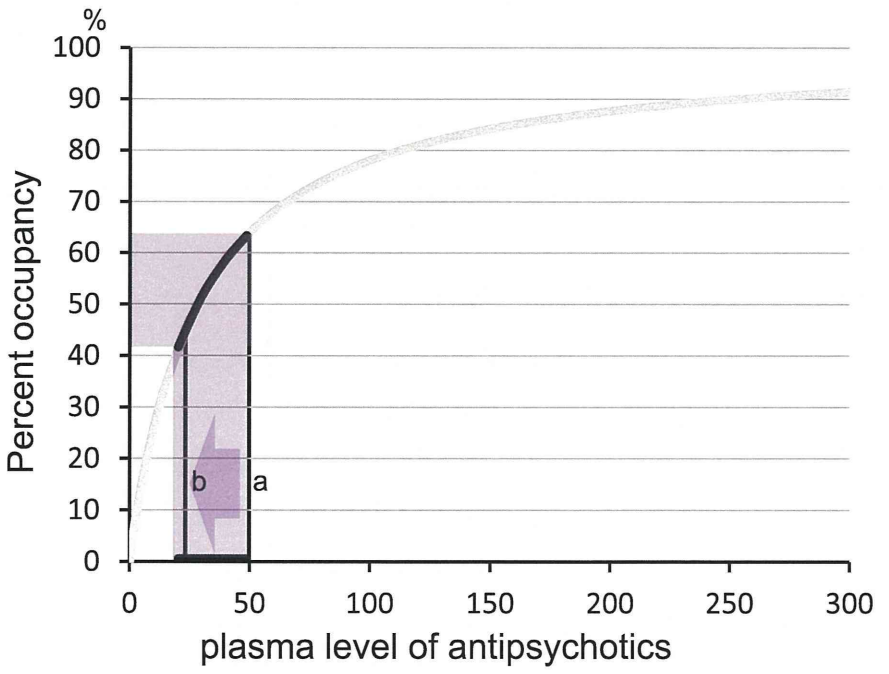
Fig.2C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Ⅳ. 添付資料

「ドパミン過感受性精神病シンポジウム」

平成 24 年 10 月 21 日（日）

平成24年10月21日(日)
ホテル ザ・マンハッタン

ドパミン過感受性精神病シンポジウム

～治療抵抗性統合失調症の治療・予防法の追求～

統合失調症薬物療法における

ドパミンD2受容体密度と至適占拠率

千葉大学大学院医学研究院
精神医学　伊豫雅臣

本日の内容

第一章　統合失調症治療における抗精神病薬のドパミンD2受容体占拠率のPETによる測定

第二章　ドパミン過感受性精神病とドパミンD2受容体密度

第三章　ドパミンD2受容体密度と至適占拠率

第四章　ドパミン過感受性精神病の予防

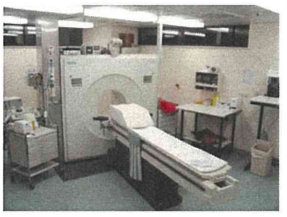
第五章　ドパミン過感受性精神病の治療

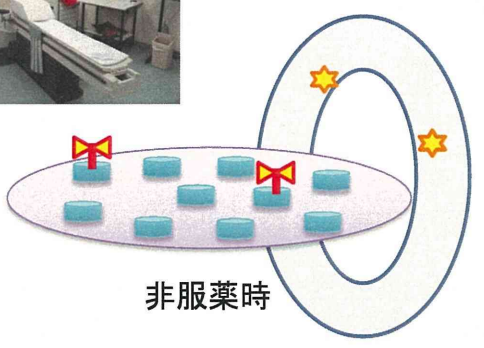
第六章　その他のD2受容体密度偏移に関わる病態

第一章

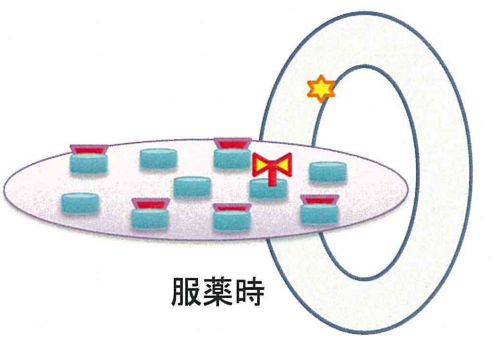
統合失調症治療における
抗精神病薬のドパミンD2受容体占拠率のPETによる測定

PETによる占拠率の測定





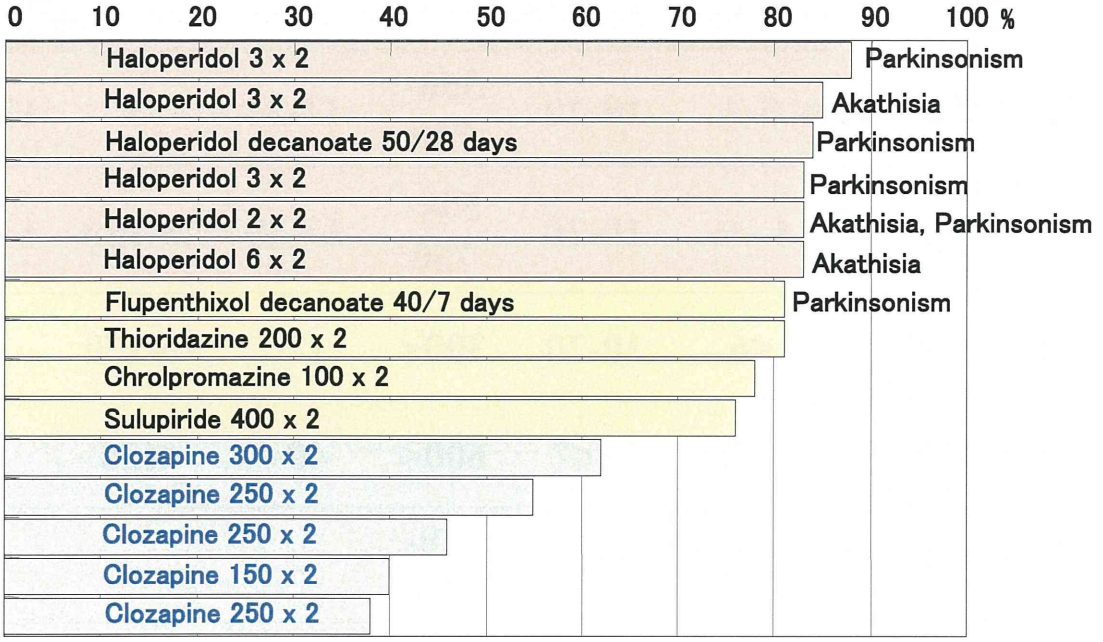
例えば、1000個の受容体



500個の受容体を薬が占拠

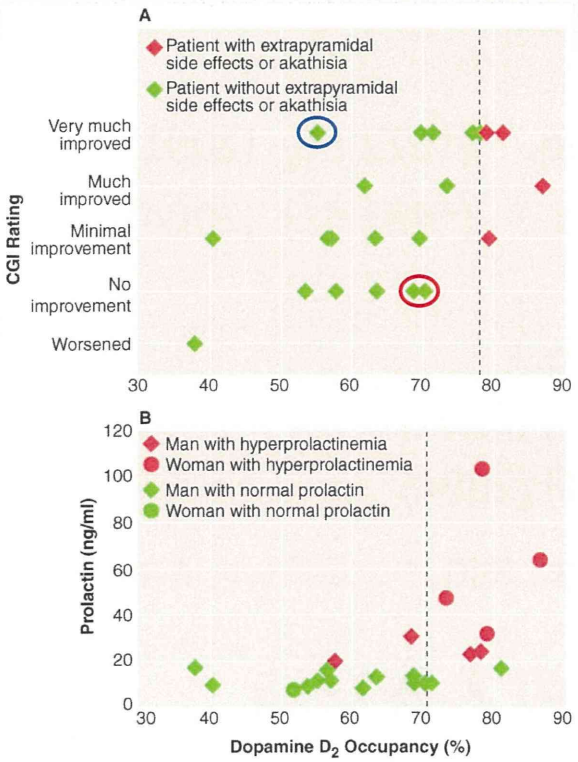
$$占拠率＝\frac{非服薬時の結合能－内服時の結合能}{非服薬時の結合能}\ X100$$

抗精神病薬の脳内D2受容体占拠率と錐体外路症状



Farde L, Wiesel FA, Halldin C, Sedvall G. Arch Gen Psychiatry. 1988 Jan;45(1):71-6.

Relationship Between Dopamine D_2 Occupancy, Clinical Response, and Side Effects: A Double-Blind PET Study of First-Episode Schizophrenia



Am J Psychiatry. 2000;157(4):514-520.

The likelihood of clinical response, hyperprolactinemia, and extrapyramidal side effects increased significantly as D(2) occupancy exceeded 65%, 72%, and 78%, respectively.

臨床的反応、高プロラクチン血症、錐体外路症状はそれぞれ、D2受容体占拠率が65%、72%、78%を超えたときであった。

ガイドランにみる各抗精神病薬処方量の目安 (mg / 日)

	RIS	OLZ	QTP	PER	ZOT	ARP
初回エピソード	3-4	10-20	350-700	12-24	75	15-30
反復例 急性期	4→6	10-20	500-750	12-48	75-150	15-30
維持期	<6	10-20	300<	12?	75-150	15
治療抵抗性	<12	20<?	600<	40<	<450	?
NMEDR	2-4	16<	150-600	-	-	

NMEDR :Near-maximal effective dose range（最大効果近接用量）
臨床精神薬理　8:1175-1277，2005より抜粋

我が国における抗精神病薬処方

Sim K, et al., BJCP, 2008

1．平均用量

1033.80±884.3 0mg CPZ eq.　(*672.86) (2001)

524.10±516.93 mgCPZ eq.　(*482.41) (2004)

2．%高用量（＞1000　mg CPZ eq.）

36.5 %.　(*17.9 %) (2001)

8.9 %　(* 6.5 %) (2004)

*中国、香港、日本、韓国、シンガポール、台湾の平均

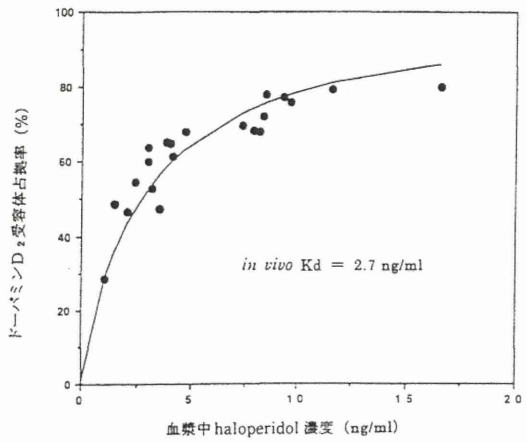
地域ナンバーワンの大量療法

PETにより測定したハロペリドール血漿中濃度とD2受容体占拠率の相関

Biol Psychiatry. 1988 Apr 1;23(7):653-63.

Serial [18F]N-methylspiroperidol PET studies to measure changes in antipsychotic drug D-2 receptor occupancy in schizophrenic patients.

Smith M, Wolf AP, Brodie JD, et al.



$$占拠率 = \frac{非服薬時の結合能 - 内服時の結合能}{非服薬時の結合能} \times 100$$

（ミカエリス・メンテンの質量保存則）

$$= \frac{1}{1 + \frac{In\ vivo\ Kd}{血漿中薬物濃度}} \times 100$$

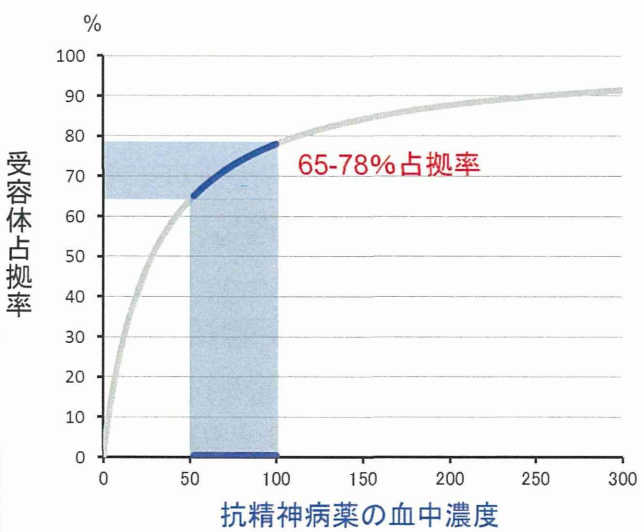
Iyo, et al., Biol. Psychiatry, 1990.

占拠率の測定と治療域

抗精神病薬の至適D2受容体占拠率（治療域）

占拠率は薬物の血漿中濃度に依存する

大量投与患者における至適占拠率（治療域）は？



$$占拠率 = \frac{1}{1 + \frac{In\ vivo\ Kd}{血漿中薬物濃度}} \times 100$$

第二章

ドパミン過感受性精神病と
ドパミンD2受容体密度

症例

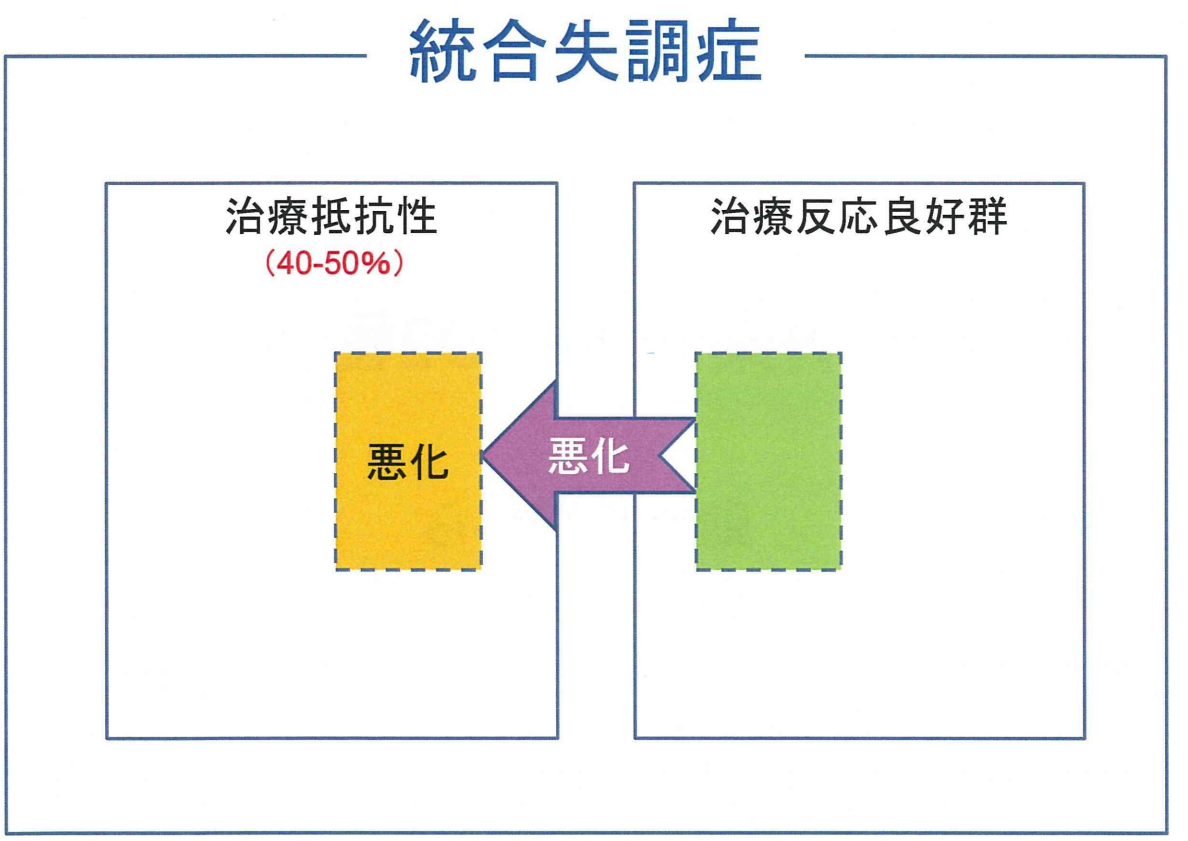
- 38歳　男性　統合失調症
- 20歳の専門学校在籍時に幻覚妄想状態にて発症。ハロペリドール（HDL）6mgで2か月程度で寛解に至った。なお、錐体外路症状のために抗コリン薬も併用していた。暫くして専門学校中退したが、アルバイトを開始した。
- しかし、22歳時に服薬中断により幻覚妄想再燃し、HDLが9mgに増量された。以降、再発を繰り返し、その度に抗精神病薬は増量された。
- しかし、36歳頃からHDL 18mg、リスペリドン12mg、クエチアピン200mgを処方するも幻覚妄想の改善は乏しくなってきた。
- 38歳時に幻覚妄想、興奮著明なため入院して保護室に隔離した。家族によれば服薬はしていたとのことであった。さらにオランザピン20mgを追加したところ、1週間程度で幻覚妄想は残遺するも興奮はみられなくなったため、ホールで1時間の開放観察することとした。ホールにいる時には興奮みられなかった。
- しかし、その夜から幻覚妄想増悪し、連合弛緩は顕著で刺激性も亢進し、開放観察が困難となった。

ドパミン過感受性精神病

Dopamine Supersensitivity Psychosis：DSP

頻度は22～43% (Schooler and Kane, 1982、Chouinard, 1988)

- 初期の抗精神病薬治療で精神病症状は改善する
- **再発・再燃**時には、**治療初期よりも抗精神病薬増量**が必要となる
- 徐々に高用量の抗精神病薬が必要となり、**精神症状改善まで長期間**を要するようになる
- 抗精神病薬の**僅かな減量や服薬中断**により容易に精神病症状が**再燃**する
- **些細なストレス**で容易に精神病症状が再燃する
- 上記のように、**治療抵抗性統合失調症**に発展し、**再発準備性**も高まる
- **治療初期の錐体外路症状の出現や遅発性ジスキネジア**が重要な予測因子である
- **D2受容体数の増加**が関与していると考えられている
- **適切な治療法は確立していない**



治療抵抗性統合失調症
Treatment-Resistant Schizophrenia

- 統合失調症患者の40-50%は治療抵抗性患者（Pantelis C and Lambert T. ,2006）
- クロザピンが有効だが、重篤な副作用があり、さらに治療効果は30-50%の治療抵抗性患者にしか認められない（ Nose M et al., 2009）

治療抵抗性統合失調症患者の50%がドパミン過感受性精神病に関連していると推定される。

Chouinard G, Chouinard VA.
Psychother Psychosom.2008;77(2):69-77.

抗精神病薬投与とD2密度変化

動物実験から