

Decreased binding of [¹¹C]NNC112 and [¹¹C]SCH23390 in patients with chronic schizophrenia

Jun Kosaka ^{a,b}, Hidehiko Takahashi ^a, Hiroshi Ito ^a, Akihiro Takano ^a, Yota Fujimura ^a, Ryohei Matsumoto ^a, Shoko Nozaki ^a, Fumihiko Yasuno ^a, Yoshiro Okubo ^c, Toshifumi Kishimoto ^b, Tetsuya Suhara ^{a,*}

^a Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

^b Department of Psychiatry, Nara Medical University, 840, Shijo-cho, Kashihara-shi, Nara 634-8521, Japan

^c Department of Neuropsychiatry, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan

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ABSTRACT

Aims: Abnormality of cognitive function in schizophrenia has been suggested to be related to dopamine D₁ receptor. However, the results of previous positron emission tomography (PET) studies of dopamine D₁ receptor in schizophrenia were not consistent.

Main methods: In this study, six patients with schizophrenia in severe residual phase with chronic antipsychotic treatment and twelve healthy age-matched controls participated. Two different radioligands, [¹¹C]NNC112 and [¹¹C]SCH23390, for dopamine D₁ receptor were used on the same subjects. Binding of the ligands was measured by PET, and statistical analysis was performed using one-way analysis of covariate (ANCOVA) with age as covariate.

Key findings: Good correlations between binding potential values (BP_{ND}) and age were observed in all regions of interest (ROIs) with both ligands. ANCOVA with age as covariate of BP_{ND} values of all ROIs revealed that the patient group showed significantly lower BP_{ND} value compared with the control group in both ligands.

Significance: In patients with chronic schizophrenia in severe residual phase with chronic antipsychotic treatment, the binding potential values of both ligands were significantly lower in the striatum and cortical regions than those of healthy controls.

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Introduction

Schizophrenia is a chronic illness characterized by positive, negative, cognitive and affective symptoms (Schultz and Andreasen 1999). Although a positive symptom is characteristic of schizophrenia in the acute phase, the characteristic symptoms in the severe residual phase are negative symptom and cognitive dysfunction. The dopamine hypothesis is widely accepted for the pathophysiology of schizophrenia. Regarding dopamine receptors, the density of dopamine D₁ receptor in the cortical region is several times higher than that of dopamine D₂ receptor (Lidow et al. 1998). Abnormality of cognitive function in schizophrenia has been suggested to be related to dopamine function in the prefrontal cortex (Sawaguchi and Goldman-Rakic 1991). Dopamine D₁ receptor plays important roles in cognitive function such as working memory (Goldman-Rakic, 2000). One postmortem study has reported low dopamine D₁ receptors in the striatum in patients with schizophrenia (Hess et al. 1987), but no significant change has been reported in other studies (Seeman et al. 1987; Czudek and Reynolds 1988; Knable et al. 1994). In vivo PET studies reported decreased (Okubo et al. 1997),

unaltered (Karlsson et al. 2002), and increased (Abi-Dargham et al. 2002) binding of D₁ receptor in patients with schizophrenia compared with control subjects. Those results were possibly influenced by parameters of the particular patient populations including duration of illness, symptoms and medications. In addition, differences in radioligand [¹¹C]SCH23390 (Okubo et al. 1997; Karlsson et al. 2002) and [¹¹C]NNC112 (Abi-Dargham et al. 2002) were suggested to account for inconsistent PET findings. Furthermore, subjects were medication-free or -naïve patients with schizophrenia in the prodromal, acute or active phase, and the duration of untreated illness may have influenced the difference in dopamine D₁ receptor binding in previous human PET studies.

The purpose of the present study was to compare the dopamine D₁ receptor binding of chronic patients with schizophrenia in severe residual phase with chronic antipsychotic treatment to that of healthy controls in the striatum and extrastriatal regions using both [¹¹C]SCH23390 and [¹¹C]NNC112 in the same subjects.

Materials and methods

Subjects

Six patients with schizophrenia, 1 female and 5 males aged 46.5 ± 8.2 years (mean ± SD), participated in this study (Table 1). All patients

* Corresponding author. Tel.: +81 43 206 3251; fax: +81 43 253 0396.
E-mail address: suhara@nirs.go.jp (T. Suhara).

Table 1
Clinical characteristics of patients.

Patient no.	Age (years)	Gender	Diagnosis (DSM-IV)	Dose of sulpiride (mg)	Duration of illness (years)	PANSS			
						Positive	Negative	General	Total
1	32	M	295.30	1200	15	16	21	30	67
2	45	F	295.30	600	28	25	26	49	100
3	47	M	295.30	1200	8	18	23	44	85
4	47	M	295.30	1000	25	23	26	47	96
5	52	M	295.10	1200	5	13	33	46	92
6	56	M	295.60	600	29	20	43	59	122
Mean \pm SD	46.5 \pm 8.2			966.7 \pm 294.4	18.3 \pm 10.5	19.2 \pm 4.4	28.7 \pm 8.1	45.8 \pm 9.4	93.7 \pm 18.1

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; PANSS, Positive and Negative Scale for Schizophrenia; M, Male; F, Female.

met the criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) for diagnosis of schizophrenia. The diagnosis was assessed by Structured Clinical Interview for DSM-IV by three psychiatrists. The patients underwent general medical and laboratory evaluation. Organic brain disease was ruled out by CT, T1-weighted magnetic resonance (MR) images, and electroencephalogram.

Prior to this study, they had been prescribed antipsychotics during the periods indicated as 'duration of illness' in Table 1. In chlorpromazine equivalents, daily doses ranged from 200 mg to 606 mg and mean dose was 384 ± 139 mg/day (Inagaki and Inada 2006).

In all patients, the previously used antipsychotic drugs were changed to sulpiride, a selective dopamine D₂/D₃ receptor antagonist without affinity to dopamine D₁ receptor. PET scans were performed after a washout period of at least three weeks after changing to sulpiride. Sulpiride was maintained at the same dosage during the washout period. Because of extrapyramidal side effects, two patients were administered a relatively low dose of sulpiride (600 mg), although there had been no exacerbation of their psychic symptoms. All patients underwent clinical ratings of their psychopathology using the positive and negative syndrome scale (PANSS; Kay et al. 1987), and the following cognitive function tests: Wisconsin Card Sorting Test (Heaton 1981) to evaluate executive function, Stroop test (Cohen and Servan-Schreiber 1992) and *n*-back tasks (2-back minus 0-back using letters as stimulus; Cohen et al. 1994; Owen et al. 2005) to evaluate working memory.

The healthy control sample consisted of 6 females and 6 males, age-matched at 42.8 ± 8.5 years. Based on unstructured psychiatric screening interviews, none had a history of neurological or psychiatric illness. Organic brain disease was ruled out by T1-weighted MRI.

The study was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Sciences, Chiba, Japan. After providing a complete explanation of the study, written informed consent was obtained from all subjects.

PET and MRI procedures

All patients except patient #6 (Table 1) underwent both PET scans using [¹¹C]NNC112 and [¹¹C]SCH23390 on the same day. Patient #6 and twelve healthy controls underwent each of the PET scans with [¹¹C]NNC112 and [¹¹C]SCH23390 within several days. The PET system ECAT EXACT HR+ (CT1-Siemens, Knoxville, TN) was used for all PET studies. The system provides 63 planes with a 15.5 cm axial field of view. After a transmission scan with a ⁶⁸Ge-⁶⁸Ga source, a bolus of [¹¹C]NNC112 or [¹¹C]SCH23390 was rapidly injected into the antecubital vein with a 20-ml saline flush. Injected radioactivity and specific radioactivity were 220.5 ± 9.25 MBq and 140.0 ± 64.1 GBq/ μ mol for patients in the [¹¹C]NNC112 studies, 215.0 ± 14.1 MBq and 152.5 ± 50.6 GBq/ μ mol for controls in the [¹¹C]NNC112 studies, 200.2 ± 15.9 MBq and 59.7 ± 15.5 GBq/ μ mol for patients in the [¹¹C]SCH23390 studies, and 220.5 ± 18.1 MBq and 68.6 ± 11.0 GBq/ μ mol for controls in the [¹¹C]SCH23390 studies, respectively.

Radioactivity in the brain was measured by a series of scans for 90 min for [¹¹C]NNC112 or 60 min for [¹¹C]SCH23390, starting

immediately after the injection. During image acquisition, the subjects were instructed to lie quietly with their eyes closed and earplugs in place. Image reconstruction was performed with a Hanning filter with a cut-off frequency of 0.4, a value experientially determined for the purpose of noise reduction, resulting in a final spatial resolution of 7.5 mm FWHM (full width at half maximum).

T1-weighted MR images were acquired on Philips Gyroscan NT, 1.5 T (Philips Medical Systems, Best, The Netherlands). Scan parameters were 1-mm-thick 3D images with a transverse plane (repetition time, TR/echo time, TE 21/9.2 ms, flip angle 30°, matrix 256 \times 256, field of view (FOV) 256 \times 256), yielding 196 contiguous slices of the head.

PET data analysis

Regions of interest (ROIs) were manually drawn on the transverse slices from each subject's PET summation images referred from MRI images coregistered to the reconstructed PET images. ROIs were set to cover 3 adjacent slices for the striatum including both the caudate nucleus and the putamen, anterior cingulate, cerebellum, temporal cortex and frontal cortex including the superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus, which roughly corresponds to dorsolateral prefrontal cortex. The sets of ROIs for each section were transferred to the corresponding PET images, and time-activity curves (TACs) were obtained. The TACs of each region were analyzed using a simplified reference tissue model in a least-squares manner, in which the cerebellum was used as reference tissue (Lammertsma and Hume 1996). This procedure produced the binding potential (BP_{ND}; Innis et al. 2007) value.

Statistical analysis

Statistical analysis of the regional BP_{ND} obtained from patients with schizophrenia and healthy control subjects was performed using one-way analysis of covariance (one-way ANCOVA) with age as covariate using SPSS for Windows 16.0.2J (SPSS Inc, Chicago, Illinois, USA 2008), and post hoc Bonferroni correction was used for multiple comparisons. *p* value $< 0.05/4 = 0.0125$ was considered significant.

Results

Table 1 lists the clinical profiles of the patients. The average duration of illness after schizophrenia diagnosis was 18.3 years. Scores of the two cognitive functional tests are shown in Table 2, and significant group effects were found in each cognitive function test. Because four patients, #2, #3, #5 and #6, were not able to do *n*-back task (2 back), results were not shown in Table 2.

Significant correlations between BP_{ND} and age were observed in patients with [¹¹C]NNC112 (frontal cortex, $r = -0.924$, $p = 0.004$; striatum, $r = -0.981$, $p = 0.001$), controls with [¹¹C]NNC112 (striatum, $r = -0.886$, $p < 0.001$) and controls with [¹¹C]SCH23390 (frontal cortex, $r = -0.757$, $p = 0.004$; striatum, $r = -0.700$, $p = 0.011$). Trend

Table 2
Cognitive task scores of patients.

Patient no.	W-CST			Stroop test	
	Category	PEN	DMS	Error	Time score
1	6	0	0	0	17.4
2	2	9	5	11	46.6
3	1	7	3	1	7.4
4	5	1	1	0	5.4
5	2	14	0	2	68
6	Incapable	Incapable	Incapable	2	75
Mean \pm SD	3.2 \pm 2.2	6.2 \pm 5.8	1.8 \pm 2.2	2.7 \pm 4.2	36.6 \pm 30.8
Controls					
Mean \pm SD	4.7 \pm 1.6	1.4 \pm 2.0	0.8 \pm 1.4	0.8 \pm 1.2	5.6 \pm 4.0

W-CST, Wisconsin card sorting test; PEN, errors of nelson; DMS, difficulty in maintaining set.

level correlations were observed in other regions and patients with [^{11}C]SCH23390.

All BP_{ND} values of both ligands are shown in Fig. 1 and summarized in Table 3. ANCOVA with age as covariate ($df=1,15$) of BP_{ND} values of all ROIs revealed that the patient group showed significantly lower BP_{ND} value compared with the control group in both ligands ([^{11}C]NNC112: temporal cortex, $F=26.24$, $p<0.001$; striatum, $F=60.08$, $p<0.001$; anterior cingulate cortex, $F=9.14$, $p=0.009$; frontal cortex, $F=42.96$, $p<0.001$, [^{11}C]SCH23390: temporal cortex, $F=34.68$, $p<0.001$; striatum, $F=25.46$, $p<0.001$; anterior cingulate cortex, $F=8.91$, $p=0.009$; frontal cortex, $F=37.60$, $p<0.001$). There

was significant correlation between average BP values of [^{11}C]NNC112 weighted by ROI size and that of [^{11}C]SCH23390 ($r=0.859$; $\text{BP}_{\text{NNC}}=0.613 \text{BP}_{\text{SCH}}+0.0414$).

There was no significant correlation between BP_{ND} values and doses of antipsychotic drugs and between BP_{ND} values and PANSS scores for positive symptom, negative symptom, general symptom and total score in any of the brain regions.

Discussion

Both [^{11}C]NNC112 and [^{11}C]SCH23390 bindings in the striatum and cortical regions of patients with schizophrenia in severe residual phase were significantly lower compared with healthy controls. In previous PET studies of patients with schizophrenia who were antipsychotics-naïve or -free, BP of [^{11}C]SCH23390 was decreased (Okubo et al. 1997) or unchanged (Karlsson et al. 2002), and was increased when measured by [^{11}C]NNC112 (Abi-Dargham et al. 2002). Several differences in those studies have been discussed, including those regarding duration of illness, medications, race, severity of symptoms and radioligands. Guo et al. (2003) reported different characteristics of in vivo binding of the two radioligands in rat brain, increased [^{11}C]NNC112 binding and decreased [^3H]SCH23390 binding, following subchronic dopamine depletion with reserpine. But the inconsistent results cannot be explained solely by the difference of radiotracers, and demographics of patients might have been contributing factors.

Although [^{11}C]SCH23390 and [^{11}C]NNC112 are selective radioligands for dopamine D_1 receptor, both ligands have some affinity for 5-

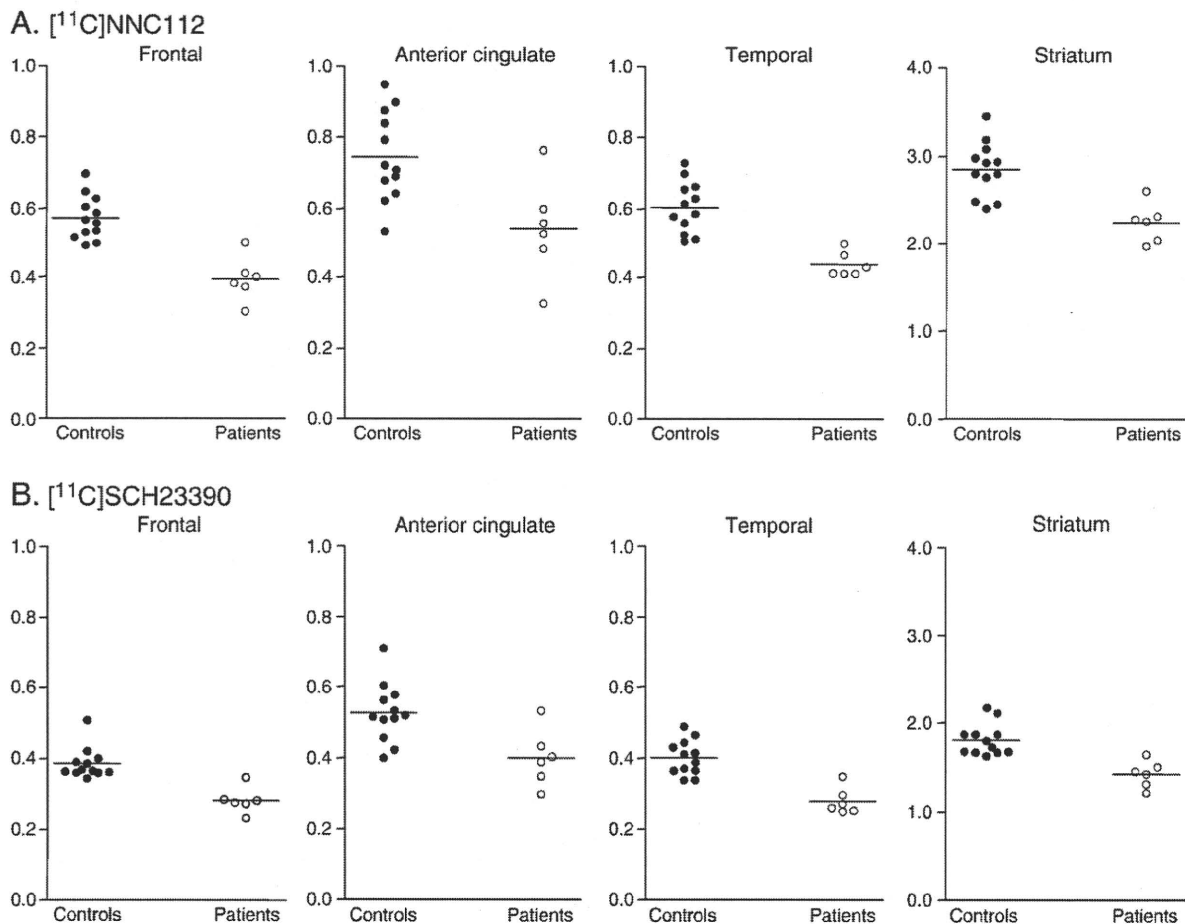


Fig. 1. BP_{ND} values of all subjects in both ligands [^{11}C] NNC112 and [^{11}C]SCH23390. Filled circles represent controls and open circles represent patients. A. BP_{ND} measured by [^{11}C] NNC112; B. BP_{ND} measured by [^{11}C]SCH23390. The horizontal line represents the group mean. In all ROIs, statistically significant differences were observed between patients with schizophrenia and healthy controls (one-way ANCOVA with age as covariate, $p<0.0125=0.05/4$).

Table 3
[¹¹C]NNC112 and [¹¹C]SCH23390 binding potential.

Region	[¹¹ C]NNC112				[¹¹ C]SCH23390			
	Controls (n = 12)	Patients (n = 6)	p value	Reduction (%)	Controls (n = 12)	Patients (n = 6)	p value	Reduction (%)
Frontal cortex	0.57 ± 0.064	0.39 ± 0.065	<0.001*	31.2	0.39 ± 0.043	0.28 ± 0.037	<0.001*	26.7
Anterior cingulate	0.75 ± 0.12	0.54 ± 0.14	0.009*	27.2	0.53 ± 0.083	0.40 ± 0.079	0.009*	23.5
Temporal cortex	0.61 ± 0.074	0.44 ± 0.037	<0.001*	27.7	0.40 ± 0.048	0.28 ± 0.038	<0.001*	29.9
Striatum	2.85 ± 0.31	2.25 ± 0.23	<0.001*	21.4	1.83 ± 0.18	1.45 ± 0.15	<0.001*	20.9

Data are mean ± SD.

* p < 0.0125 (= 0.05/4, Bonferroni corrected) ANCOVA with age as covariate (df = 1,15).

HT_{2A} receptor (Slifstein et al. 2007). However, Okubo et al. (2000) reported no difference in binding in the prefrontal cortex using [¹¹C]N-methylspiperone as ligand for 5-HT₂ receptor in the same schizophrenia patients who showed lower binding with [¹¹C]SCH23390 (Okubo et al. 1997) and a non-significant trend towards decreased binding. In this study, all patients were medicated with only sulpiride as antipsychotic drug. Sulpiride is a selective dopamine D₂ antagonist and has negligible affinity to dopamine D₁ receptor in vivo (Farde et al. 1989). All antipsychotics of the patients were changed to sulpiride. Even though sulpiride had no direct affinity to dopamine D₁ receptor, these patients had been receiving long-term chronic antipsychotic treatment. Several studies of primates have reported that chronic administration of dopamine D₂ receptor antagonist decreased the density of dopamine D₁ receptor (Lidow and Goldman-Rakic 1994; Lidow et al. 1997), although one animal study has reported that there was no influence of chronic medication on dopamine D₁ receptor density (Sanci et al. 2002). Hirvonen et al. (2006) reported a widespread reduction of D₁ receptor binding in the brain in patients with schizophrenia, which was associated with antipsychotic medication dose. However, we did not find a correlation between them, possibly due to a lack of variance in antipsychotic dose.

The patients in this study were in a very severe residual phase according to the deficits in the cognitive test scores (Table 2) and the high total scores of PANSS despite the low positive symptom scores (Table 1). Some studies have reported regional structural brain abnormalities of gray matter in the striatum and extrastriatal regions of schizophrenia patients with chronic antipsychotic treatment (Jernigan et al. 1991; Tamagaki et al. 2005). In this study, since we confirmed that there was no significant difference between the volume of each ROI in patients and that of controls, we measured the gray matter volume ratio in each ROI. The results revealed no significant difference between the gray matter volume in patients and that of controls in each ROI (data not shown). The values of reduction in BP_{ND} shown by percentage (Table 3) seemed considerably larger than the reduction of gray matter. However, the effect of brain gray matter reduction cannot also be ruled out.

Our results indicated lower dopamine D₁ receptor binding in schizophrenia patients with chronic antipsychotic treatment measured by different radioligands, [¹¹C]NNC112 and [¹¹C]SCH23390. However, as the small sample size was a distinct limitation of this study, a larger study population will be necessary to more definitively examine the relation between dopamine D₁ receptor binding and factors such as duration of illness and severity of symptoms.

Conflict of interest statement

There are no conflicts of interests.

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Antiepileptic drugs and psychosis in epilepsy

Masato Matsuura

Section of Biofunctional Informatics, Graduate School of Health Care Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan

Antiepileptic drugs (AEDs) (*Table I*) affect neurotransmitter systems that are not only involved in the generation and propagation of seizure activity, but also implicated in the pathogenesis of psychiatric disorders. As such, it is not surprising that AEDs exert positive or negative effects on psychiatric status in patients with epilepsy. The psychiatric adverse effects of an AED can be seen in its dose-dependent and idiosyncratic characteristics. Dose-dependent reactions are related to the primary and secondary pharmacologic effects of the drug, and are predictable, host-independent, and resolvable with dose reduction. On the other hand, idiosyncratic reactions are host-dependent, and cannot be predicted based on the known pharmacologic effects of a drug. They do not demonstrate a simple dose-response relationship, depending at least in part on an individual's underlying neuropsychiatric state.

Psychosis, which is characterized by delusions and prominent hallucinations under clear consciousness, can represent a rare but an important complication of all AEDs. It affects the individual's ability to determine boundaries between the self and the environment to formulate effective behaviors and decisions for everyday life. The mechanisms of AED-related psychosis may be a pharmacological consequence, drug toxicity, drug withdrawal, or an alternative psychosis with forced normalization. Such psychoses are purported to result from dysfunction in a widespread neural circuit, resulting in both structural and neurochemical abnormalities. However, in particular, they are associated with biological and genetic predispositions in each epileptic individual. In the current work, a selective review of the published literature on AED-related psychosis in both English and Japanese was carried out.

■ Historical aspects

Physicians have noted both dose-dependent and idiosyncratic psychiatric side effects of AEDs. As early as 1859, Heinrich Hoffmann, a well-known physician and writer, reported that a patient with epilepsy developed psychosis after becoming seizure-free following treatment with *Extracta cotylodenis*, a commonly used herbal medication at the time, as an idiosyncratic adverse effect [4]. In 1893, when bromides constituted the mainstay of

Table I. Classifications of antiepileptic drugs and mechanisms of action

Author(s), year of publication	Classifications of AEDs	
Ketter, 1999 [1] 2 categories	Predominantly GABA mechanisms of action	Anti-glutamatergic effects
	Typical: BBs, BZs, GPT, TGB, VGB, VPA, ZNS Partial: CBZ, OXC, PHT, TPM	Typical: FBM Partial: LTG
Rogawski & Loscher, 2004 [2] 3 categories	Predominantly sodium and calcium channel activity	GABA-mediated mechanisms Mixed, complex, or poorly understood actions
	CBZ, LTG, OXC, PHT, ZNS	BZs, TGB, VGB ESM, FBM, GPT, LEV, PB, TPM, VPA
Glauser, 2004 [3] 4 categories	Voltage-gated cationic ion channel modulation	Augmentation of GABAergic transmission Mixed GABAergic and antiglutamatergic actions Other than conventional actions
	CBZ, ESM, LTG, OXC, PHT, VPA, ZNS	BBs, BZs, GBP, TGB, VGB FBM, TPM LEV

AEDs: antiepileptic drugs; barbiturates (PB: phenobarbital; PRM: primidone); benzodiazepines (CLB: clobazam; CNZ: clonazepam); CBZ: carbamazepine; ESM: ethosuccimide; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PGB: pregabalin; PHT: phenytoin; VPA: valproic acid; TGB: tiagabine; VGB: vigabatrin; FBM: felbamate; TPM: topiramate; ZNS: zonisamide.

pharmacotherapy for epilepsy as the first AED of the modern era, Gowers stated that when attacks that have occurred for many years stop suddenly, whether the stoppage is spontaneous or due to the influence of drugs, patients may become dull, forgetful, and sometimes irritable or semi-idiotic.

In 1942, when phenobarbital (PB) was introduced in epilepsy treatment, Lennox [5] reported that occasional susceptible patients may suffer either in the direction of increased slowness or of active psychosis with medication. He reported that the incidence of mental worsening with PB was 11.6%, while that with bromides was 17.5%. In 1951, Gibbs [6] stated that psychosis seen as a complication of the treatment of psychomotor seizures with phenacemide has a mechanism similar to psychotic disorders which may occur when such seizures are suppressed by other anticonvulsant agents, such as barbiturates and hydantoins.

Consideration of the concept of forced normalization and its clinical counterpart, alternative psychosis, is essential when discussing the AED-related psychosis. In 1958, Landolt [7] reported productive psychotic episodes with "forced normalization" in the EEG. He wrote that this form of twilight state readily occurs on the institution of treatment, and that cautious discontinuation of medication frequently has a favorable effect in such cases. In 1965, Tellenbach [8] introduced the term "alternative psychosis" to refer to the clinical phenomenon of a reciprocal relationship between psychosis and seizures. Several psychopathological pictures have been linked to forced normalization, and psychosis is the most common [9].

Wolf *et al.* [9] reported that the incidence of forced normalization was 12 cases (15%) of 82 absence patients treated with ESM monotherapy, compared to none in 126 patients treated with valproate (VPA) monotherapy. Although ESM appears to be more likely to relate to

forced normalization, all AEDs can produce this phenomenon. Pakalnis *et al.* [10] reported seven psychotic cases with forced normalization, six with AED monotherapy (3 carbamazepine [CBZ], 2 methsuximide, and 1 VPA), and one with co-therapy (CBZ and VPA). With regards to newer AEDs, Trimble *et al.* [11] reported a retrospective case note study on 89 patients who developed psychosis or affective disorder during AED treatment, and concluded that forced normalization appeared to relate more to the use of GABAergic drugs, particularly with more powerful agents, such as topiramate (TPM), vigabatrin (VGB), and tiagabine (TGB).

Psychoses are often seen in a setting in which previously refractory patients suddenly become seizure-free. This phenomenon is not restricted to AED-induced seizure control. It is likely that in patients who develop *de novo* psychosis following epilepsy surgery, forced normalization may play such a role. A case of an alternative psychosis secondary to vagus nerve stimulation has been reported [12]. A rare case, which showed spontaneous seizure remission and the alternating emergence of psychotic symptoms, was reported in Japan [13].

■ Prevalence of AED-related psychosis

It is difficult to estimate the exact prevalence of AED-related psychosis. Because there are no systematic data with respect to older AEDs, retrospective clinical series and case reports should be included to estimate the prevalence of older AED-related psychosis. While many randomized controlled clinical trials for the newer AEDs are present, they are designed to test anti-seizure efficacy and have failed to use standardized psychiatric diagnostic criteria. Another problem regards the inconsistency of the definition of psychosis in the AED-related psychosis literature. Some reports have been based on standardized criteria for psychosis, such as the ICD-10 or DSM-IV, while others have adopted an in-house criterion of psychosis, and many others have used the term without definition. The follow-up should be long enough to differentiate between AED-related effects and the natural course of the comorbid disorder. An exact method to determine whether an AED is causing a psychosis would be to withdraw the drug, and subsequently rechallenge with it and observe the outcome. However, such studies have ethical limitations.

Although treatment emergent psychosis tends to be seen by all AEDs in those who are susceptible to developing psychosis, certain AEDs appear to be more likely to be associated with a psychosis. Kawasaki *et al.* [14] analyzed the association between AEDs and psychosis of epilepsy based on 26 Japanese patients, and concluded that the most relevant drugs were high-dose phenytoin (PHT) and zonisamide (ZNS). Cockerell *et al.* [15] surveyed the neurologists in the UK, and 19 cases were reported to have acute psychological disorders, including psychosis. They reported that VGB was the most commonly identified, followed by lamotrigine (LTG). Matsuura [16] analyzed 44 consecutive patients with epilepsy and acute psychosis, and reported that 17 cases (39%) were AED-related psychosis, and that adjunctive ZNS therapy was the most commonly attributed. Schmitz [17] analyzed 26 epilepsy patients with psychosis, and reported that four cases (16%) were AED-related, caused mainly by polytherapy with PHT.

Brodtkorb & Mula [18] recommended that VGB, TPM, ethosuccimide (ESM), and ZNS should be avoided in patients vulnerable to psychosis, and that levetiracetam (LEV) should be used with caution and benzodiazepines (BZD), gabapentin (GBP), and pregabalin (PGB) should be considered. According to the incidence of reported cases with AED-associated psychosis, three AED groups, frequently, moderately, and rarely associated with psychosis, might be distinguished.

■ AEDs frequently associated with psychosis (*Table II*)

Table II. AEDs frequently reported to induce psychosis (single case reports are omitted)

1. Suicimides	
Fisher <i>et al.</i> , 1965 [19]	3 cases (2.9%) with 5 episodes of hallucinatory psychosis; disappeared after discontinuation of ESM
Wolf <i>et al.</i> , 1984 [9]	8 absence patients (3.5%) showed psychosis and forced normalization with ESM
Pakalnis <i>et al.</i> , 1987 [10]	2 TLE patients showed psychosis and forced normalization with methsuximide
2. TPM	
Crawford, 1998 [20]	11 cases (12%) showed psychotic symptoms with add-on therapy
Khan <i>et al.</i> , 1999 [21]	5 psychotic cases (0.8%) soon after starting the drug; symptoms resolved quickly after discontinuation or dose reduction
Trimble <i>et al.</i> , 2000 [11]	18 patients developed psychosis (5 post-ictal, 5 seizure suppression or reduction, 3 seizure increased, 5 seizure unchanged)
Stella <i>et al.</i> , 2002 [22]	2 cases with acute psychosis; full remission after interruption or reduction of dose
Kanner <i>et al.</i> , 2003 [23]	9 cases (1.5%) in a prospective multi-center study
Mula <i>et al.</i> , 2003 [24]	16 cases (3.7%) in a prospective study, mainly postictal psychosis, followed by alternative psychosis, and schizophrenia-like psychosis
Reith <i>et al.</i> , 2003 [25]	10 children and adolescents (6%) showed aggression or psychosis
Grosso <i>et al.</i> , 2005 [26]	6 children and adolescents (2%) showed acute psychosis in a study of long-term treatment
3. VGB	
Sander <i>et al.</i> , 1991 [27]	14 cases with intractable epilepsy with psychosis (including 4 post-ictal, 4 alternative, 1 overdose)
Cockerell <i>et al.</i> , 1996 [15]	4 cases with acute psychosis (3 with seizure improvement, 1 with seizure aggravation)
Thomas <i>et al.</i> , 1996 [28]	28 cases with psychosis, characterized by severe epilepsy, higher dose, right-sided focus, and seizure freedom
Trimble <i>et al.</i> , 2000 [11]	28 patients developed psychosis (including 7 post-ictal, 16 alternative)
4. ZNS	
Kawasaki <i>et al.</i> , 1991 [14]*	7 TLE cases with polytherapy; 5 experienced within 1 month, 3 were alternative psychosis
Matsuura <i>et al.</i> , 1993 [29]*	8 cases (6 TLE, 2 FLE) with polytherapy; 3 were alternative psychosis and 2 post-ictal psychosis
Hara <i>et al.</i> , 1993 [30]*	5 TLE cases with polytherapy; average latency of psychosis was 6 months, 3 were alternative psychosis
Mayahara <i>et al.</i> , 1995 [31]*	3 TLE cases with alternative psychosis, one with monotherapy
Miyamoto <i>et al.</i> , 2000 [32]	14 cases (19%) in a retrospective study; 7 developed psychosis within 1 year, alternative factors may have contributed

* In Japanese.

FLE: frontal lobe epilepsy; TLE: temporal lobe epilepsy.

Succinamides: ethosuccimide and methsuximide

ESM modifies the properties of voltage-dependent calcium channels, reducing T-type currents and thereby preventing synchronized firing. Fisher *et al.* [19] reported that three patients (2.8%) in 105 epileptic patients developed five psychotic episodes occurring within a few days of ESM treatment. The EEG often reverted to normal during the psychotic episodes. Because the psychotic symptoms improved after ESM discontinuation, they considered the symptoms as exogenous psychosis. Wolf *et al.* [9] reported that 18 cases (7.8%) showed forced normalization in 229 absence patients treated with ESM mono/polytherapy, and that eight (3.5%) of these patients showed paranoid episodes. Pakalnis *et al.* [10] described two patients with complex partial seizures whose psychotic symptoms emerged shortly after starting methsuximides. The temporal lobe abnormalities present on the EEGs prior to treatment became normalized during the patients' psychotic episodes.

Topiramate

TPM was introduced into the Japanese market in 2007 for adjunctive therapy in treating partial seizures. It has a wide range of potentially anticonvulsant actions, such as an anti-glutamatergic action at AMPA/kainate receptors, blockage of voltage dependent sodium channels, potentiation of GABAergic inhibition, and carbonic anhydrase inhibition. Crawford [20] carried out an audit of TPM use at a general neurology clinic, and 11 cases (12%) of 94 patients were identified as having psychotic symptoms, which was significantly higher than that for patients treated with other AEDs. Khan *et al.* [21] reported that five patients (0.8%) showed psychotic symptoms soon after beginning TPM with the dose of 50-400 mg, and that these symptoms resolved quickly after discontinuation or dose reduction of TPM. Trimble *et al.* [11] reported 18 cases with TPM-related psychosis, and stated that the low dose group developed with a shorter interval between the start of the TPM therapy and the onset of psychosis, compared with the high dose groups. Kanner *et al.* [23] conducted a prospective multi-center study, and reported that the prevalence of TPM-induced psychosis in polytherapy regimens was 9 cases (1.5%) of 596 patients, and that patients with a past psychiatric history present a higher risk of experiencing psychiatric as well as cognitive adverse events. Mula *et al.* [24] conducted a prospective study of 431 patients treated with TPM to determine the prevalence of psychiatric events. Sixteen patients (3.7%) were reported to have had psychotic disorders, mainly postictal psychosis (1.7%), followed by alternative psychosis (1.1%), and schizophrenia-like psychosis (0.9%). They concluded that the risk factors were high starting dose, rapid titration, a psychiatric history, and more severe epilepsy with a high seizure frequency.

Reith *et al.* [25] conducted a retrospective cohort study of 159 patients aged less than 18 years, and reported that 10 cases (6%) developed aggression or psychosis, especially in those with a history of prior aggression. Grosso *et al.* [26] reported that acute psychosis occurred in 6 patients (2%) in a study of the long-term treatment of 277 children and adolescents. Therefore, TPM may itself induce psychosis in susceptible patients, and slow dose titration may reduce the risk of this side effect.

Vigabatrin (VGB)

VGB is a structural analogue of GABA, which exerts its anticonvulsant action by irreversibly binding to GABA transaminase, blocking degradation of GABA and increasing its concentration in the brain. It was never approved for use in Japan, due to

evidence of irreversible peripheral visual field loss in a portion of patients with chronic use. Sander *et al.* [27] reported a series of 14 cases of psychosis occurring in patients with severe intractable epilepsy, following the prescription of VGB with a polytherapy regimen. Four developed psychosis after seizure freedom (alternative psychosis), while the other four developed after a period of seizure freedom followed by a cluster of seizures (postictal psychosis). The period to the onset of psychosis was 5 days to 32 weeks, and all resolved on withdrawal. They stated that VGB had powerful antiepileptic action and should be started with caution in patients with a previous history of psychosis. Ferrie *et al.* [33] reviewed seven placebo-controlled European studies and showed an overall occurrence of psychosis of 3.4% in the VGB group and 0.6% in the placebo group. Levinson & Devinsky [34] conducted another meta-analysis of double-blind studies, and demonstrated that psychosis occurred 2.5% in the VGB group compared to 0.3% in the placebo group. Thomas *et al.* [28] reported 28 cases with VGB-treatment emergent psychosis, and concluded that the risk factors were severe epilepsy, right-sided focus, suppression of seizures, and a history of psychosis compared with the VGB-induced depression group. Psychosis may be caused by a direct pharmacological action of VGB, or through indirect mechanisms which may arise from its effects on seizure control.

Zonisamide

ZNS has been approved since 1987 in Japan for partial epilepsy. It has a number of different effects in the brain which may be responsible for its anticonvulsant effects, including blockage of T-type calcium channels, inhibition of sodium channels, possible inhibition of glutamate release, and also mild inhibition of carbonic anhydrase. Matsuura & Trimble [35] reviewed five Japanese papers on ZNS-associated psychosis, and estimated the prevalence at 2%. Miyamoto *et al.* [32] identified 14 epileptic patients (19%) with psychotic episodes in a total of 74 young patients, in a retrospective study on ZNS treatment over a 10-year period. Because 7 patients developed psychosis a few years after the initiation of ZNS treatment, they stated that alternative factors may have caused or contributed to the development of psychosis. ZNS enhances dopamine transmission and was approved for use in Parkinson disease in 2008 in Japan. Its dopamine effect may also contribute to the induction of psychosis in epilepsy.

■ AEDs moderately associated with psychosis (*Table III*)

Table III. AEDs sometimes reported to induce psychosis (single case reports are omitted)

1. Barbiturates, benzodiazepines	
Demers-Desrosiers <i>et al.</i> , 1978 [36]	2 cases with psychotic symptoms immediately after withdrawal of AEDs including PB and PRM
Kugoh <i>et al.</i> , 1990 [37]	2 psychotic cases with toxic PB serum levels
Sironi <i>et al.</i> , 1979 [38]	2 cases with acute psychosis as a CZP withdrawal syndrome
Hauser <i>et al.</i> , 1989 [39]	3 cases with BZ withdrawal delirium with catatonic features
2. LTG	
Crawford, 1998 [20]	2 psychotic cases (0.7%) with add-on therapy

Clemens, 2005 [40]	2 psychotic cases (a child with BECT and an adult with TLE) with forced normalization
Brandt <i>et al.</i> , 2007 [41]	6 cases (0.4%) with schizophrenia-like psychosis; risk factors are high dose, temporal lobe pathology, and past psychiatric history
3. LEV	
Kossoff <i>et al.</i> , 2001 [42]	1 child and 3 adolescent cases with psychosis; all had previous behavior problems or cognitive deficit
Mula <i>et al.</i> , 2003 [43]	6 psychotic cases (1.2%) in a prospective study
4. PHT	
Franks & Richter, 1979 [44]	2 cases with psychotic symptoms as an organic brain syndrome
Kawasaki <i>et al.</i> , 1991 [14]*	4 TLE cases with psychosis (3 were alternative psychosis with high-dose monotherapy)
Sengoku <i>et al.</i> , 1991 [45]*	2 TLE cases of alternative psychosis with high-dose monotherapy
Watanabe <i>et al.</i> , 1994 [46]*	4 alternative psychosis cases with high-dose therapy
5. TGB	
Cockerell <i>et al.</i> , 1996 [4]	2 cases with alternative paranoid psychosis
Trimble <i>et al.</i> , 2000 [11]	3 cases with psychosis
Sackellares <i>et al.</i> , 2002 [47]	3 cases (0.8%) with psychotic symptoms with add-on therapy, in a multi-center, double-blind, placebo-controlled trial

* In Japanese.

BECT: benign epilepsy of children with centro-temporal spikes; TLE: temporal lobe epilepsy.

Barbiturates: phenobarbital and primidone

The anticonvulsant action of Barbiturates is probably related to their enhancement of GABA-mediated inhibition. Twenty to 40% of children being treated with PB developed a behavior disorder, such as hyperactivity, depression, irritability, and aggressiveness [48]. In adults, a high dose of PB could induce psychosis [37]. Primidone (PRM) is also reported to produce acute psychotic symptoms, including bizarre and hallucinatory behavior immediately after administration [48]. Demers-Desrosiers *et al.* [36] reported two cases of patients with epilepsy who became psychotic immediately after withdrawal of AEDs, including PB and PRM. These psychoses occurred in the context of clear sensorium, accompanied by markedly increased EEG abnormalities, and recovered completely within days after the reinstatement of medication. Kanner *et al.* [49] have emphasized that interictal psychiatric symptoms worsened in severity during the postictal period, and that 19 patients taking one AED with negative psychotropic properties (PB, PRM, or VGB) yielded a trend towards a greater likelihood of developing postictal psychosis.

Benzodiazepines

Benzodiazepines and barbiturates enhance GABAergic inhibition by interacting directly with GABA-A receptors. Withdrawal syndrome with prominent psychiatric symptoms including psychosis can occur with barbiturates and benzodiazepines. Sironi *et al.* [38]

reported two patients with temporal lobe epilepsy and acute psychosis manifesting as CZP withdrawal syndrome. They stated that the patients' psychomotor seizures disappeared, and depth EEG recording showed a marked reduction of repetitive abnormalities during the psychotic state (forced normalization). Hauser *et al.* [39] reported three cases with delirium and catatonic symptoms as benzodiazepine withdrawal syndrome (clorazepate dispotassium, 2 patients; CZP, 1 patient). On the other hand, Franks & Richter [44] reported three cases with schizophrenia-like psychosis associated with AED toxicity, and one of these developed delusional and hallucinatory behavior after an overdose of CZP.

Lamotrigine

LTG is a generally well-tolerated drug with broad-spectrum efficacy and was approved as an adjunctive treatment for partial epilepsy in 2008 in Japan. LTG probably exerts its anticonvulsant effects *via* a combination of sodium channel inhibition and calcium channel effects. Sporadic case reports have appeared of psychosis attributed to LTG treatment. The incidence of psychotic symptoms in 270 patients taking LTG in a general neurology clinic was 0.7% [20]. Clemens [40] reported two cases with LTG-induced forced normalization, and a reduction of LTG led to the disappearance of the symptoms and the reappearance of spikes on their EEGs. Brandt *et al.* [41] reported six cases with schizophrenia-like psychotic disorders, the symptoms of which improved rapidly after discontinuing LTG or decreasing the dose. They reported that one patient who was re-exposed to LTG again presented similar symptoms.

Levetiracetam

LEV has a specific CNS-limited binding site unique among AEDs, and its exact mechanism is unknown. Although the drug is generally well tolerated, behavioral side effects have been reported with variable frequency. Mula *et al.* [43] prospectively studied psychiatric adverse events during LEV therapy, and reported psychiatric adverse events in 53 cases (10.1%) from 517 patients, among which were 6 cases (1.2%) with psychosis. Cramer *et al.* [50] conducted a meta-analysis, and reported that the prevalence of psychosis was 1.4%. Regarding children and adolescents, Kossoff *et al.* [42] reported one child and three adolescents with LEV treatment-emergent frank psychosis. All of these patients had behavior problems or cognitive deficits before initiating LEV, and all experienced dramatic improvement within days of either discontinuing or decreasing the dose of LEV.

Phenytoin

The anticonvulsant effect of PHT is related to sodium channel blockade. Several anecdotal case reports have appeared of high dose PHT-related psychosis. Franks & Richter [44] reported two cases with psychotic symptoms characterized by clear sensorium with minimal signs of toxicity, classed as PHT organic brain syndrome. Kawasaki *et al.* [14] reported four cases of temporal lobe epilepsy which developed PHT-related psychosis, three of which were alternative psychosis with high-dose monotherapy. Watanabe *et al.* [46] reported four psychotic cases with PHT high-dose treatment. All of these patients exhibited schizophrenia-like psychosis with clear consciousness and epileptiform discharges on their EEGs.

Tiagabine

TGB inhibits neuronal and glial GABA reuptake, thereby enhancing GABA's inhibitory effect. Because TGB has a mechanism of action similar to that of VGB, concern has been raised regarding its potential to cause treatment-emergent psychosis. Sackellares *et al.* [47] conducted an ad hoc analysis of two multi-center, randomized, double-blind, placebo-controlled studies of add-on therapy of TGB, and 3 cases (0.8%) of 356 TGB-treated patients developed psychosis, compared to none of 198 placebo-treated patients. Cockerell *et al.* [15] reported two psychotic cases. Trimble *et al.* [11] reported three cases with TGB-related psychosis.

■ AEDs rarely associated with psychosis (Table IV)

Table IV. AEDs rarely reported to induce psychosis (single case reports are included)

1. CBZ	
Franks & Richter, 1979 [44]	1 case with psychotic symptoms exacerbated by rechallenge
Pakalnis <i>et al.</i> , 1987 [10]	4 psychotic cases with forced normalization (3 monotherapy and 1 co-therapy with VPA)
Mathew, 1988 [51]	1 case with epilepsy and mild mental handicap; psychosis developed shortly after change from VPA
McKee <i>et al.</i> , 1989 [52]	1 case with acute psychotic reaction shortly after add-on therapy
Samuimi-Ardestani <i>et al.</i> , 2008 [53]	1 TLE case with hallucinatory symptom; disappeared with discontinuation
2. FBM	
Knable & Kenneth, 1995 [54]	1 case with long-standing hypoxic brain damage developed severe psychotic symptoms
McConnell <i>et al.</i> , 1996 [55]	1 case with psychosis
3. GBP/PGB	
Crawford, 1998 [20]	1 case (0.5%) with GBP add-on therapy
Olaizola <i>et al.</i> , 2006 [56]	1 case with psychotic symptoms with PGB
4. VP	
Pakalnis <i>et al.</i> , 1987 [10]	2 psychotic cases with forced normalization (1 absence patient with monotherapy, 1 TLE patient with co-therapy with CBZ)

TLE: temporal lobe epilepsy

Carbamazepine and oxcarbazepine

These AEDs probably exert their anticonvulsant effects by sodium channel blockade, though they also have other sites of action. CBZ is approved for use in Japan for the manic state an excited state of schizophrenia. On the other hand, its prescribing information designates that the drug can provoke hallucinations and/or excitations. Rare but sporadic epilepsy cases with CBZ-related psychosis were reported as a direct side effect [44, 51-53] or forced normalization [10].

Although no previous studies have reported psychosis as a side effect of OXC, a case with Parkinson disease which developed psychotic symptoms, probably through the dopamine agonistic mechanism of OXC, was reported [57].

FBM

FBM has a number of anti-excitatory effects, which account for its anticonvulsant effects, including that on NMDA and non-NMDA excitatory amino acid receptors, as well as the inhibition of voltage-gated sodium channels. It is rarely used at present, due to serious hepatic and hematological adverse effects in some patients. Rare but sporadic epileptic patients with treatment related psychosis have been reported when receiving FEL monotherapy [55] or FBM add-on therapy [54].

Gabapentin and pregabalin

Despite being analogs of GABA, the anticonvulsant actions of GBP and PGL are likely to not be related to effects on the usual GABA binding sites. Their mechanism of action remains unknown. In the audit of the use of AEDs in a general neurology clinic carried out by Crawford [20], one case (0.5%) of 191 patients receiving GPT add-on therapy exhibited psychotic symptoms. A 44-year-old female with acute psychosis associated with marked EEG exacerbation after rapid titration of a relatively large dose of PGL was also reported [56].

Valproate

The mechanism of action of VPA may include the potentiation of GABAergic functions and inhibition of voltage-sensitive sodium channels. VPA is approved for use in Japan for the manic state and behavior disorders of epilepsy, such as dysphoria and/or aggression. Pakalnis *et al.* [10] reported two psychotic cases; one with VPA monotherapy, and one with cotherapy with VPA and CBZ. They considered these to be induced by forced normalization and not as a direct effect of VPA.

■ Mechanisms of AED-induced psychosis

Ketter [1] has classified AEDs into those with predominantly GABA mechanisms of action and those with antiglutamatergic effects (*Table I*). Rogawski & Loscher [2] have categorized AEDs into three categories: (1) predominant sodium (and calcium) channel activity; (2) GABA-mediated mechanisms; and (3) mixed, complex or poorly understood actions (*Table I*). Glauser [3] has grouped AEDs into four broad categories based on their major mechanisms of action: (1) voltage-gated cationic ion channel modulation; (2) augmentation of GABAergic transmission; (3) mixed GABAergic and antiglutamatergic actions; and (4) other than conventional actions (*Table I*). All of these classifications of AEDs do not correlate with the rate of treatment-emergent psychosis, and AED-related psychosis seems to occur irrespective of the mechanisms of action of the AED.

Matsuura [16] reported 17 patients with AED-related psychosis, including seven following rapid titration, six after acute discontinuation, and four after taking an overdose of AEDs. The follow-up study revealed that six showed recurrent psychosis without a clear relationship with any AED, and one showed a chronic course of psychosis. Schmidt *et al.* [17] analyzed 26 epileptic patients with AED-related psychosis, and reported that 8% were alternative, 4% withdrawal, and 4% intoxication from AEDs. Weintraub *et al.* [58]

reported that the average rate of AED-related psychopathology for a single AED was 8.4%, with 6.1% resulting in dose change and 4.3% resulting in AED discontinuation. It appears that psychoses with the newer AEDs occurred frequently in early clinical trials, involving a dosing schedule that subsequently appeared to be rapid, or doses that were too high. Because rapid changes in the regimen of powerful AEDs induce psychosis, it can be argued that the underlying pathomechanisms are common. A dramatic alteration in the balance between inhibitory and excitatory processes, a deficit of homeostasis in the brain, may play a key role in AED-related psychosis.

■ Conclusion

A selective review of the published literature in English and Japanese on AED-related psychosis was carried out. All AEDs can induce treatment-induced psychosis, regardless of the mechanisms of action, and it can be argued that the underlying pathomechanism is common. Because rapid changes in the regimen of powerful AEDs induce acute psychosis, a dramatic alteration in the balance between inhibitory and excitatory processes may play a key role. AED-induced psychosis is typically transient and responsive to a reduction or discontinuation of the drug or to antipsychotic treatment. Although it may be rare, psychosis can reoccur without relating to medication or persist chronically. When prolonged overinhibition persists, recurrent or chronic psychosis may occur. Powerful AEDs should be used with a slow titration schedule and with monotherapy, especially those prone to develop psychosis.

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Sleep-related problems and use of hypnotics in inpatients of acute hospital wards

Minori Enomoto, B.Sc.^{a,c}, Takako Tsutsui, Ph.D.^b, Sadanori Higashino, Ph.D.^b,
Masaaki Otaga, M.S.W.^b, Shigekazu Higuchi, Ph.D.^a, Sayaka Aritake, Ph.D.^a,
Akiko Hida, Ph.D.^a, Miyuki Tamura, Ph.D.^a,
Masato Matsuura, M.D., Ph.D.^c, Yoshitaka Kaneita, M.D., Ph.D.^d,
Kiyohisa Takahashi, M.D., Ph.D.^e, Kazuo Mishima, M.D., Ph.D.^{a,*}

^aDepartment of Psychophysiology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo 187-8553, Japan

^bDepartment of Social Services, National Institute of Public Health, Ministry of Health, Labour and Welfare, Saitama 351-0197, Japan

^cSection of Biofunctional informatics, Graduate School of Health Care Sciences, Tokyo Medical and Dental University, Tokyo 113-8519, Japan

^dDivision of Public Health, Department of Social Medicine, Nihon University School of Medicine, Tokyo 173-8610, Japan

^eAino University, Osaka 567-0012, Japan

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Abstract

Objective: Although sleep disorders are highly prevalent among patients with physical disorders, only limited information is available about the actual status of sleep-related problems in inpatients of acute hospital wards. We conducted a multicenter cross-sectional observational survey investigating the prevalence of sleep disorders and use of hypnotic-sedative drugs among inpatients of acute wards in 44 general hospitals in Japan.

Method: Questionnaire-, actigraph- and observation-based sleep evaluations were simultaneously performed in 557 adult inpatients [mean age 72.8±12.8 (S.D.) years] of acute wards during a one-month period in July 2007.

Results: Of the 421 patients with data available, 22.3% had at least one of the following sleep disorders: sleep apnea syndrome, restless legs syndrome, periodic limb movement disorder and nocturnal behavior disorder. Similarly, 62.7% had insomnia, 6.9% had severe daytime sleepiness and 12.8% had other sleep-related symptoms. Only 13.8% were free of any sleep-related problem. Although 33.7% of insomnia patients were taking hypnotic-sedative drugs, 65.2% of them complained of residual insomnia symptoms.

Conclusion: The findings obtained in this study have revealed the remarkably high prevalence of sleep-related problems experienced by inpatients of acute hospital wards in Japan. Proper diagnosis of sleep disorders should be made among patients with physical disorders.

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Keywords: Sleep disorders; Insomnia; Acute hospital wards; Physical illness; Hypnotic use

1. Introduction

Sleep disorders, including insomnia, sleep apnea syndrome (SAS), restless legs syndrome (RLS) and periodic limb movement disorder (PLMD), are highly prevalent and particularly common in elderly patients with physical disorders. Sleep disorders reduce patients' quality of life (QOL) by causing symptoms such as daytime sleepiness and cognitive impairment and may also exacerbate underlying disorders by inhibiting respiratory, cardiovascular and

* Corresponding author. Tel.: +81 42 346 2014; fax : +81 42 346 2072.

E-mail addresses: minori@ncnp.go.jp (M. Enomoto), tsutsui@niph.go.jp (T. Tsutsui), sadanori@u-shizuoka-ken.ac.jp (S. Higashino), otaga@niph.go.jp (M. Otaga), shige@ncnp.go.jp (S. Higuchi), sayaca@ncnp.go.jp (S. Aritake), hida@ncnp.go.jp (A. Hida), tamuram@ncnp.go.jp (M. Tamura), matsu.mtec@tmd.ac.jp (M. Matsuura), kaneita@med.nihon-u.ac.jp (Y. Kaneita), ktaka@ncnp.go.jp (K. Takahashi), mishima@ncnp.go.jp (K. Mishima).

metabolic functions. In one study of older patients in a skilled-care geriatric hospital in Japan, the presence of insomnia was associated with a higher risk of mortality during the 2-year follow-up period [1].

The prevalence of these sleep disorders increases with age [2], and the high incidence of physical disorders among the elderly population is a contributing factor. Previous epidemiologic studies have revealed that the prevalence of insomnia among the general population is 10.2–48.0% [3–6], and insomnia frequently occurs in association with chronic pain disorders, respiratory diseases and neurological diseases [7]. SAS, RLS or PLMD also frequently coexists with various physical diseases including hypertension [8], ischemic heart disease [9,10], chronic kidney failure [11], iron-deficiency anemia [12] and neurological diseases such as Parkinson's disease [13]. It is also noteworthy that medications used for the treatment of sleep disorders may worsen physical disorders; for example, most standard hypnotics benzodiazepines cause *sleep apnea* by reducing the muscle tone of the upper respiratory tract during sleep [14].

The fact that physical and sleep disorders can coexist at a high frequency should always be taken into account when making an accurate diagnosis and developing a treatment strategy that provides a favorable risk-benefit balance. Nevertheless, we currently have only limited information about the actual status of sleep-related problems experienced by inpatients of acute hospital wards. Thus, the objectives of the present study were to investigate the breakdown and prevalence of sleep disorders and use of hypnotic-sedative drugs in acute ward inpatients and to identify problems in the clinical practice of sleep medicine.

2. Methods

2.1. Subjects and method

Study subjects who were 20 years of age or more were randomly selected from among the inpatients of acute hospital wards, excluding psychiatric and tuberculosis wards, of 44 general hospitals in Japan. The patients'

identities were coded at each hospital ward, and then patients were randomly sampled. The investigation was carried out among 557 subjects [316 males, 241 females; mean age, 72.8±12.8 (S.D.) years; range 22–96 years] who had provided informed consent or whose family member had provided informed consent, simultaneously at all hospitals during a period of 1 month in July 2007. Each patient's primary disorder was classified according to the International Classification of Diseases and Related Health Problems Version 10 (*ICD-10*) (Table 1). The ethics committee at each research site approved the present study.

2.2. Investigation methods

The investigation was conducted over 2 days for each patient to check his or her sleep condition and details of treatment. The investigation consisted of subjective sleep evaluation using a self-administered questionnaire (Table 2), objective sleep evaluation by actigraphy, observational sleep evaluation by nursing staff and a survey of medication use as recorded in the medical records.

The questionnaire was designed to identify the presence of insomnia, SAS, RLS, PLMD, nocturnal behavior disorder (NBD), daytime sleepiness and nocturnal sleep-related symptoms. In the questionnaire, Q1–Q6 were completed by the patients, and Q7 and Q8 were completed by medical staff. Although NBD can be further divided into nocturnal delirium, REM sleep behavior disorder, behavioral and psychological symptoms of dementia and other symptoms, these disorders were not distinguished in view of the primary objective of the present study and technical restrictions.

For objective sleep evaluation, subjects were asked to wear an actigraph [Lifecorder PLUS (LC), Suzuken, Nagoya, Japan] [15] on their waist for two consecutive days for continuous recording of the intensity of activity. Total sleep time (TST; the sum of all sleep time during time in bed), total wake time (TWT; the sum of all wake time during time in bed) and sleep efficiency (SE; the percentage of TST relative to time in bed) were then calculated from the LC data. Time in bed (TIB) was defined as the time during

Table 1
Illness identified in enrolled patients

System organ/disease class	Total 557 (100%)	SAS, RLS, PLMD and NBD 94 (100%)	Insomnia			Good Sleep 63 (100%)
			Improved 31 (100%)	Untreated 175 (100%)	Not-Improved 58 (100%)	
Diseases of the circulatory system	140 (25.1)	20 (21.3)	7 (22.6)	44 (25.1)	9 (15.5)	15 (23.8)
Neoplasms	127 (22.8)	19 (20.2)	5 (16.1)	47 (26.9)	26 (44.8)	8 (12.7)
Diseases of the respiratory system	68 (12.2)	11 (11.7)	3 (9.7)	17 (9.7)	8 (13.8)	9 (14.3)
Diseases of the digestive system	62 (11.1)	13 (13.8)	2 (6.5)	21 (12.0)	7 (12.1)	8 (12.7)
Diseases of the nervous system	45 (8.1)	11 (11.7)	2 (6.5)	9 (5.1)	3 (5.2)	5 (7.9)
Diseases of the genitourinary system	16 (2.9)	4 (4.3)	1 (3.2)	5 (2.9)	1 (1.7)	3 (4.9)
Diseases of the musculoskeletal system and connective tissue	14 (2.5)	2 (2.1)	1 (3.2)	7 (4.0)	0 (0.0)	3 (4.9)
Certain infectious and parasitic diseases	8 (1.4)	0 (0.0)	1 (3.2)	3 (1.7)	1 (1.7)	0 (0.0)
Other diseases	77 (13.8)	14 (14.9)	9 (29.0)	22 (12.6)	3 (5.2)	12 (19.0)

SAS; sleep apnea syndrome, RLS; restless legs syndrome, PLMD; periodic limb movement disorder, NBD; nocturnal behavior disorder.