Table 3
[^{11}C] NNC112 and [^{11}C]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 [^{11}C]N-methylspiperone as ligand for 5-HT2 receptor in the same schizophrenia patients who showed lower binding with [^{11}C]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 D_2 antagonist and has negligible affinity to dopamine D_1 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 D_1 receptor, these patients had been receiving long-term chronic antipsychotic treatment. Several studies of primates have reported that chronic administration of dopamine D_2 receptor antagonist decreased the density of dopamine D_1 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 D_1 receptor density (Sanci et al. 2002). Hirvonen et al. (2006) reported a widespread reduction of D_1 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 D_1 receptor binding in schizophrenia patients with chronic antipsychotic treatment measured by different radioligands, [^{11}C]NNC112 and [^{11}C]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 D_1 receptor binding and factors such as duration of illness and severity of symptoms.

Conflict of interest statement

There are no conflicts of interests.

Acknowledgements

This study was supported by a consignment expense for the Molecular Imaging Program on "Research Base for PET Diagnosis" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government. The sponsors of the study had no role in the study design, collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

We thank Mr. Takahiro Shiraishi and Mr. Akira Ando for their assistance in performing the PET experiments at the National Institute of Radiological Sciences. We also thank Ms. Yoshiko Fukushima of the National Institute of Radiological Sciences for her help as clinical research coordinator, and Miho Shidahara is acknowledged for her valuable comments.

References

Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DR, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M. Prefrontal dopamine D1 receptors and working memory in schizophrenia. The Journal of Neuroscience 22 (9), 3708–3719, 2002.

Cohen JD, Servan-Schreiber D. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychological Review 99, 45–77, 1992.

Cohen JD, Forman SD, Braver TS, Casey BJ, Servan-Schreiber D, Noll DC. Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. Human Brain Mapping 1, 293–304, 1994.

Czudek C, Reynolds G. Binding of [11C]SCH 23390 to post-mortem brain tissue in schizophrenia. British Journal of Pharmacology 93, 166P suppl, 1988.

Farde L, Wiesel FA, Nordström AL, Sedvall G. D1- and D2-dopamine receptor occupancy during treatment with conventional and atypical neuroleptics. Psychopharmacology (Berl) 99, S28–S31 Suppl, 1989.

Goldman-Rakic PS, Muly 3rd EC, Williams GV. D1 receptors in prefrontal cells and circuits. Brain Research Reviews 31 (2–3), 295–301, 2000.

Guo N, Hwang DR, Lo ES, Huang YY, Laruelle M, Abi-Dargham A. Dopamine depletion and in vivo binding of PET D1 receptor radioligands: implications for imaging studies in schizophrenia. Neuropsychopharmacology 28 (9), 1703–1711, 2003.

Heaton RK. A Manual for the Wisconsin Card Sorting Test. Psychological Assessment Resources, Odessa, FL, 1981.

Hess EJ, Bracha HS, Kleinman JE, Creese I. Dopamine receptor subtype imbalance in schizophrenia. Life Sciences 40 (15), 1487–1497, 1987.

Hirvonen J, van Erp TG, Huttunen J, Aalto S, Någren K, Huttunen M, Lönnqvist J, Kaprio J, Cannon TD, Hietala J. Brain dopamine D1 receptors in twins discordant for schizophrenia. The American Journal of Psychiatry 163 (10), 1747–1753, 2006.

Inagaki A, Inada T. Dose equivalence of psychotropic drugs: 2006-version. Rinsyou Seisihn Yakuri (Clinical Psychopharmachology) 9, 1443–1447 in Japanese, 2006.

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. Journal of Cerebral Blood Flow and Metabolism 27 (9), 1533–1539, 2007.

Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Braff DL. Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. Archives General Psychiatry 48 (10), 881–890, 1991.

Karlsson P, Farde L, Halldin C, Sedvall G. PET study of D1 dopamine receptor binding in neuroleptic-naïve patients with schizophrenia. The American Journal of Psychiatry 159 (5), 761–767, 2002.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13 (2), 261–276, 1987.

Knable MB, Hyde TM, Herman MM, Carter JM, Bigelow L, Kleinman JE. Quantitative autoradiography of dopamine-D1 receptors, D2 receptors, and dopamine uptake sites in postmortem striatal specimens from schizophrenic patients. Biological Psychiatry 36 (12), 827–835, 1994.

Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. Neuroimage 4 (3 Pt 1), 153–158, 1996.

Lidow MS, Goldman-Rakic PS. A common action of clozapine, haloperidol, and remoxipride on D1- and D2-dopaminergic receptors in the primate cerebral cortex. Proceedings of the Natlional Academy Sciences of the U.S.A. 91, 4353–4356, 1994.

Lidow MS, Elsworth JD, Goldman-Rakic PS. Down-regulation of the D1 and D5 dopamine receptors in the primate prefrontal cortex by chronic treatment with antipsychotic drugs. The Journal of Pharmacology and Experimental Therapeutics 281 (1), 597–603, 1997.

Lidow MS, Williams GV, Goldman-Rakic PS. The cerebral cortex: a case for a common site of action of antipsychotics. Trends in Pharmacological Sciences 19 (4), 136–140, 1998.

Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature 385 (6617), 634–636, 1997.

Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M. Serotonin 5-HT2 receptors in schizophrenic patients studied by positron emission tomography. Life Sciences 66 (25), 2455–2464, 2000.

Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Human Brain Mapping 25 (1), 46–59, 2005.

Sanci V, Houle S, DaSilva JN. No change in dopamine D1 receptor in vivo binding in rats after sub-chronic haloperidol treatment. Canadian Journal of Physiology and Pharmacology 80 (1), 36–41, 2002.

Sawaguchi T, Goldman-Rakic PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 251 (4996), 947–950, 1991.

Schultz SK, Andreasen NC. Schizophrenia. Lancet 353 (9162), 1425–1430, 1999.

Seeman P, Bzowej NH, Guan HC, Bergeron C, Reynolds GP, Bird ED, Riederer P, Jellinger K, Tourtellotte WW. Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's, and Huntington's diseases. Neuropsychopharmacology 1 (1), 5–15, 1987.

Slifstein M, Kegeles LS, Gonzales R, Frankle WG, Xu X, Laruelle M, Abi-Dargham A. [^{11}C]NNC 112 selectivity for dopamine D1 and serotonin 5-HT(2A) receptors: a PET study in healthy human subjects. Journal of Cerebral Blood Flow and Metabolism 27 (10), 1733–1741, 2007.

Tamagaki C, Sedvall GC, Jönsson EG, Okugawa G, Hall H, Pauli S, Agartz I. Altered white matter/gray matter proportions in the striatum of patients with schizophrenia: a volumetric MRI study. The American Journal of Psychiatry 162 (12), 2315–2321, 2005.

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 antigultamateric 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. Suiccimides	
Fisher *et al.*, 1965 [19]	3 cases (2.9%) with 5 episodes of hallucinatory psychosis; disappeared after discontinuation of ESM
Wolf *et al.*, 1984 [9]	8 absence patients (3.5%) showed psychosis and forced normalization with ESM
Pakalnis *et al.*, 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 *et al.*, 1999 [21]	5 psychotic cases (0.8%) soon after starting the drug; symptoms resolved quickly after discontinuation or dose reduction
Trimble *et al.*, 2000 [11]	18 patients developed psychosis (5 post-ictal, 5 seizure suppression or reduction, 3 seizure increased, 5 seizure unchanged)
Stella *et al.*, 2002 [22]	2 cases with acute psychosis; full remission after interruption or reduction of dose
Kanner *et al.*, 2003 [23]	9 cases (1.5%) in a prospective multi-center study
Mula *et al.*, 2003 [24]	16 cases (3.7%) in a prospective study, mainly postictal psychosis, followed by alternative psychosis, and schizophrenia-like psychosis
Reith *et al.*, 2003 [25]	10 children and adolescents (6%) showed aggression or psychosis
Grosso *et al.*, 2005 [26]	6 children and adolescents (2%) showed acute psychosis in a study of long-term treatment
3. VGB	
Sander *et al.*, 1991 [27]	14 cases with intractable epilepsy with psychosis (including 4 post-ictal, 4 alternative, 1 overdose)
Cockerell *et al.*, 1996 [15]	4 cases with acute psychosis (3 with seizure improvement, 1 with seizure aggravation)
Thomas *et al.*, 1996 [28]	28 cases with psychosis, characterized by severe epilepsy, higher dose, right-sided focus, and seizure freedom
Trimble *et al.*, 2000 [11]	28 patients developed psychosis (including 7 post-ictal, 16 alternative)
4. ZNS	
Kawasaki *et al.*, 1991 [14]*	7 TLE cases with polytherapy; 5 experienced within 1 month, 3 were alternative psychosis
Matsuura *et al.*, 1993 [29]*	8 cases (6 TLE, 2 FLE) with polytherapy; 3 were alternative psychosis and 2 post-ictal psychosis
Hara *et al.*, 1993 [30]*	5 TLE cases with polytherapy; average latency of psychosis was 6 months, 3 were alternative psychosis
Mayahara *et al.*, 1995 [31]*	3 TLE cases with alternative psychosis, one with monotherapy
Miyamoto *et al.*, 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 VBG-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 *et al.*, 1978 [36]	2 cases with psychotic symptoms immediately after withdrawal of AEDs including PB and PRM
Kugoh *et al.*, 1990 [37]	2 psychotic cases with toxic PB serum levels
Sironi *et al.*, 1979 [38]	2 cases with acute psychosis as a CZP withdrawal syndrome
Hauser *et al.*, 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 *et al.*, 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 *et al.*, 2001 [42]	1 child and 3 adolescent cases with psychosis; all had previous behavior problems or cognitive deficit
Mula *et al.*, 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 *et al.*, 1991 [14]*	4 TLE cases with psychosis (3 were alternative psychosis with high-dose monotherapy)
Sengoku *et al.*, 1991 [45]*	2 TLE cases of alternative psychosis with high-dose monotherapy
Watanabe *et al.*, 1994 [46]*	4 alternative psychosis cases with high-dose therapy
5. TGB	
Cockerell *et al.*, 1996 [4]	2 cases with alternative paranoid psychosis
Trimble *et al.*, 2000 [11]	3 cases with psychosis
Sackellares *et al.*, 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 reinstitution 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 patents' 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] conduced 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 *et al.*, 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 *et al.*, 1989 [52]	1 case with acute psychotic reaction shortly after add-on therapy
Samuimi-Ardestani *et al.*, 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 *et al.*, 1996 [55]	1 case with psychosis
3. GBP/PGB	
Crawford, 1998 [20]	1 case (0.5%) with GBP add-on therapy
Olaizola *et al.*, 2006 [56]	1 case with psychotic symptoms with PGB
4. VP	
Pakalnis *et al.*, 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 antigultamateric 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.

References ***[[To the author: please check ref. 8]]***

1. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. *Neurology* 1999; 53 (suppl 2): S53-67.
2. Rogawski MA, Loscher W. The neurobiology of antiepileptic drugs. *Nature* 2004; 5: 553-64.
3. Glauser TA. Effects of antiepileptic medications on psychiatric and behavioral comobidities in children and adolescents with epilepsy. *Epilepsy Behav* 2004; 5: S25-S32.
4. Schmidt B. Forced normalization: History of a concept. In: Trimble MR, Schmitz B, eds. *Forced Normalization and Alternative Psychoses of Epilepsy*. Petersfield: Wrightson Biomed Publ Ltd, 1998: 7-24.
5. Lennox WG. Brain injury, drugs, and environment as causes of mental decay in epilepsy. *Am J Psychiatry* 1942; 99: 174-80.
6. Gibbs FA. Ictal and non-ictal psychiatric disorders in temporal lobe epilepsy. *J Nerv Ment Dis* 1951; 113: 522-8.
7. Landolt H. Serial electroencephalographic investigation during psychotic episodes in epileptic patients and during schizophrenic attacks. In: Lorenz de Haes AM, ed. *Lectures on Epilepsy*. Amsterdam: Elsevier, 1958: 91-133.
8. Tellenbach H. Epilepsie als Anfallsleiden und als Psychose. U"ber alternative Psychosen paranoider Pra"gung bei "forcierter Normalisierung" (Landolt) des Elektroenzephalogramms Epileptischer. *Nervenarzt* 1965; 36: 190-202.
9. Wolf P, Inoue Y, Röder-Wanner U, *et al*. Psychiatric complications of absence therapy and their relation to alteration of sleep. *Epilepsia* 1984; 25: S56-S59.
10. Pakalnis A, Drake ME, John K, *et al*. Forced normalization: Acute psychosis after seizure control in seven patients. *Arch Neurol* 1987; 44: 289-92.

11. Trimble MR, Rusch N, Betts T, *et al.* Psychiatric symptoms after therapy with new antiepileptic drugs: psychopathological and seizure related variables. *Seizure* 2000; 9: 249-54.
12. Gatzonis SD, Stamboulis E, Siafakas A, *et al.* Acute psychosis and EEG normalization after vagus nerve stimulation. *J Neurol Neurosurg Psychiatry* 2000; 69: 278-9.
13. Minabe Y, Kurachi M: A case of epilepsy with "forced normalization" without antiepileptic treatment. *Seishin-Igaku* 1990; 32: 196-8.
14. Kawasaki J, Sengoku A, Kanemoto K, *et al.* Two occurrences of acute paranoid-hallucinatory state in epilepsy; in association with antiepileptic drugs. *Seishin-Igaku* 1991; 32: 595-600.
15. Cockerell OC, Moriatry J, Trimble M, *et al.* Acute psychological disorders in patients with epilepsy: a nation-wide study. *Epilepsy Res* 1996; 25: 119-31.
16. Matsuura M. Epileptic psychoses and anticonvulsant drug treatment. *Journal of Neurology, Neurosurgery and Psychiatry* 1999; 67: 231-3.
17. Schmitz B, Robertson MM, Trimble MR. Depression and schizophrenia in epilepsy: social and biological risk factors. *Epilepsy Res* 1999; 35: 59-68.
18. Brodtkorb E, Mula M. Optimizing therapy of seizures in adult patients with psychiatric comorbidity. *Neurology* 2006; 67 (suppl 4): S39-S44.
19. Fisher M, Korskjaer G, Pedersen E. Psychotic episodes in Zarondan treatment. *Epilepsia* 1965; 6: 325-34.
20. Crawford P. An audit of topiramate use in a general neurology clinic. *Seizure* 1998; 7: 207-11.
21. Khan A, Faught E, Gilliam F, *et al.* Acute psychotic symptoms induced by topiramate. *Seizure* 1999; 8: 235-7.
22. Stella F, Caetano D, Cendes F, *et al.* Acute psychotic disorders induced by topiramate. *Arq Neuropsiquiatr* 2002; 60: 285-7.
23. Kanner AM, Wuu J, Faught E, *et al.* A past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. *Epilepsy Behav* 2003; 4: 548-52.
24. Mula M, Trimble MR, Lhatoo SD, *et al.* Topiramate and psychiatric adverse events in patients with epilepsy. *Epilepsia* 2003; 44: 659-63.
25. Reith D, Burke C, Appleton DB, *et al.* Torelability of topiramate in children and adolescents. *J Paediatr Child Health* 2003; 39: 416-9.
26. Grosso S, Franzoni E, Iannetti P, *et al.* Efficacy and safety of topiramate in refractory epilepsy of childhood: long-term follow-up study. *J Child Neurol* 2005; 20: 893-7.
27. Sander JW, Hart YM, Trimble MR, *et al.* Vigabatrin and psychosis. *J Neurol Neurosurg Psychiatry* 1991; 54; 435-9.
28. Thomas L, Trimble MR, Schmitz B, *et al.* Vigabatrin and behaviour disorders: a retrospective survey. *Epilepsy Res* 1996; 25: 21-7.
29. Matsuura M, Senzaki A, Okubo Y, *et al.* Eight epileptic patients showing delusional-hallucinatory state during zonisamide administration. *Seishin-Igaku* 1993; 35: 413-9.
30. Hara S, Imasaka Y, Takei S, *et al.* Five cases of zonisamide-related psychosis: with particular reference to the drug interaction between zonisamide and phenytoin and to the risk factors for epileptic psychosis. *Seishinka-Chiryogaku* 1993; 8: 59-64.
31. Mayahara K, Kanemoto K, Kawasaki J, *et al.* Zonisamide and epileptic psychosis. *Tenkan-Kenkyu* 1995; 13: 177-83.
32. Miyamoto T, Kohsaka M, Koyama T. Psychotic episodes during zonisamide treatment. *Seizure* 2000; 9: 65-70.
33. Ferrie CD, Robinson RO, Panayiotopoulos CP. Psychiatric and severe behavioural reactions with vigabatrin: a review. *Acta Neuro Scand* 1996; 93: 1-8.
34. Levinson DF, Devinsky O: Psychiatric adverse events during vigabatrin therapy. *Neurology* 1999; 53: 1503-11.

35. Matsuura M, Trimble MR: Zonisamide and psychoses. *J Epilepsy* 1997; 10: 52-4.
36. Demers-Desrosiers LA, Nestoros JN, Vaillancourt P. Acute psychosis precipitated by withdrawal of anticonvulsant medication. *Am J Psychiatry* 1978; 135: 981-3.
37. Kugoh T, Inoue T, Utsumi T, *et al.* Five epileptic cases who manifested psychotic states under the toxic levels of antiepileptic drugs. *Jpn J Psychiat Neurol* 1990; 44: 392-3.
38. Sironi VA, Franzini A, Ravagnati L, *et al.* Interictal acute psychosis in temporal lobe epilepsy during withdrawal of anticonvulsant therapy. *J Neurol Neurosurg Psychiatry* 1979; 42: 724-30.
39. Hauser P, Devinsky O, De Bellis M, *et al.* Benzodiazepine withdrawal delirium with catatonic features. *Arch Neurol* 1989; 46: 696-9.
40. Clemens B. Forced normalization precipitated by lamotrigine. *Seizure* 2005; 14: 485-9.
41. Brandt C, Fueratsch N, Boehme V, *et al.* Development of psychosis in patients with epilepsy treated with lamotrigine: report of six cases and a review of literature. *Epilepsy Behav* 2007; 11: 133-9.
42. Kossoff EH, Bergey GK, Freeman JM, *et al.* Levetiracetam psychosis in children with epilepsy. *Epilepsia* 2001; 42: 1611-3.
43. Mula M, Trimble MR, Yuen A, *et al.* Psychiatric adverse events during levetiracetam therapy. *Neurology* 2003; 61: 704-6.
44. Franks RD, Richter AJ: Schizophrenia-like psychosis associated with anticonvulsant toxicity. *Am J Psychiatry* 1979; 136: 973-4.
45. Sengoku A, Kawasaki J, Kanemoto K, *et al.* High-dose monotherapy of phenytoin for intractable temporal lobe epilepsy. *Tenkan-Kenkyu* 1991; 9: 117-23.
46. Watanabe M, Kugoh T, Akada K, *et al.* High serum level therapy of phenytoin in epilepsy. *Seishinka-Chiryogaku* 1994; 9: 729-36.
47. Sackellares JC, Krauss G, Sommerville KW, *et al.* Occurrence of psychosis in patients with epilepsy randomized to tiagabine or placebo treatment. *Epilepsia* 2002; 43: 394-8.
48. Vining EPG. Use of barbiturates and benzodiazepines in treatment of epilepsy. *Neurol Clin* 1986; 4: 617-32.
49. Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. *Neurology* 2004; 62: 708-13.
50. Cramer JA, de Rue K, Devinsky O, *et al.* A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials. *Epilepsy Behav* 2003; 4: 124-32.
51. Mathew G. Psychiatric symptoms associated with carbamazepine. *BMJ* 1988; 296: 1071.
52. McKee RJW, Larkin JG, Brodie MJ. Acute psychosis with carbamazepine and sodium valproate. *Lancet Jan* 1989; 21: 167.
53. Samuimi-Ardestani SM, Zahiroddin A, Khodaifar F, *et al.* Epilepsy presenting panic attacks and hallucinatory experiences as drug side effect: a case report. *Ann Gen Psychiatry* 2008; 7: S119.
54. Knable MB, Rickler K. Psychosis associated with felbamate treatment. *J Clinical Psycho* 1995; 15: 292-3.
55. McConnell H, Snyder PJ, Duffy JD, *et al.* Neuropsychiatric side effects related to treatment with felbamate. *J Neuropsychiatry Clin Neurosci* 1996; 8: 341-6.
56. Olaizola I, Ellger T, Young P, *et al.* Pregabalin-associated acute psychosis and epileptiform EEG-changes. *Seizure* 2006; 15: 208-10.
57. Kovacs N, Nagy F, Balas I, *et al.* Oxcarbazepine may induce psychotic symptoms in Parkinson's disease. *Epilepsy Behav* 2008; 12: 492-3.
58. Weintraub D, Buchsbaum R, Resor SR, *et al.* Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy. *Epilepsy Behav* 2007; 10: 105-10.

Available online at www.sciencedirect.com
ScienceDirect
General Hospital Psychiatry 32 (2010) 276–283
General Hospital Psychiatry

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,*]

[a]*Department of Psychophysiology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo 187-8553, Japan*
[b]*Department of Social Services, National Institute of Public Health, Ministry of Health, Labour and Welfare, Saitama 351-0197, Japan*
[c]*Section of Biofunctional informatics, Graduate School of Health Care Sciences, Tokyo Medical and Dental University, Tokyo 113-8519, Japan*
[d]*Division of Public Health, Department of Social Medicine, Nihon University School of Medicine, Tokyo 173-8610, Japan*
[e]*Aino University, Osaka 567-0012, Japan*

Received 6 November 2009; accepted 26 January 2010

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.
© 2010 Elsevier Inc. All rights reserved.

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).

0163-8343/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.genhosppsych.2010.01.015

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.

Table 2
Question items and percentages of respondents in the analyzed 421 inpatients

Items		1)	2)	3)	4)
Q1. How long did it take from light off until you went to sleep?					
1) less than 15 minutes 2) 15-29 minutes 3) 30-59 minutes 4) more than 60 minutes		50.4	20.4	14.5	14.7
Q2. How many times did you awake during last night?					
1) none 2) 1-2 times 3) 3-4 times 4) more than 5 times		21.4	35.9	24.9	17.8
Q3. What time did you get up this morning (h:min)?		22.6*	77.4		
Q4. Did you get up in the morning unrefreshed or nonrestored?					
1) good 2) fair 3) insufficient 4) poor		38.7	37.1	19.2	5.0
Q5. Do you have daytime sleepiness?**					
1) none 2)some 3) moderate 4) severe		22.8	22.8	47.5	6.9
Q6. Did you experience any of the following symptoms during last night (completed by a patient)					
Q6-a creeping sensation or restless discomfort in the limbs	1) yes 2) no	5.9	94.1		
Q6-b legs or arms jerk	1) yes 2) no	2.4	97.6		
Q6-c hot flash	1) yes 2) no	4.8	95.2		
Q6-d night sweat	1) yes 2) no	6.9	93.1		
Q6-e palpitation	1) yes 2) no	1.2	98.8		
Q6-f anxiety or panic	1) yes 2) no	1.0	99.0		
Q6-g sleep paralysis	1) yes 2) no	0.0	100.0		
Q6-h nightmare	1) yes 2) no	3.1	96.9		
Q7. Did the patient experience any of the following symptoms during last night (completed by nursing staffs)					
Q7-a loud snoring, or apnea lasting for 10 seconds or longer	1) yes 2) no	10.0	90.0		
Q7-b periodic legs or arms jerk	1) yes 2) no	2.1	97.9		
Q7-c sleep-talking, delirium or abnormal behaviors such as wandering	1) yes 2) no	6.9	93.1		
Q8. Whether or not the patient took any hypnotic-sedative drug(s) for treatment of insomnia within the past one week and the name of the drug(s) if any (completed by nursing staffs)					
1) yes 2) no Name of drugs [ ]		27.6	72.4		

* Patients who woke up 30 minutes or earlier than the desired time without falling asleep again (Q3).
** answered at 2 pm.

which patients were supposed to be in bed as specified by each hospital ward, and specifically the time from "lights out" to the time at which patients were expected to wake. Mean TIB was approximately between 9 p.m. and 6 a.m. Observations by the nursing staffs on each of the wards confirmed that the patients were in bed during TIB on the evenings of the study.

For the observational sleep evaluations, several nursing staffs alternated in order to record continuously the subjects' sleep states. Opening and closing of eyes, breathing, movement and any unusual behavior of the subjects were observed and recorded at a distance so as to not disturb the subjects.

2.3. Differential diagnosis of sleep disorders

The diagnostic flow for the patients included in the investigation is shown in Fig. 1. Some of the preselected subjects (n=136) were either excluded from data analyses or could not participate due to reasons such as sudden change in physical condition such as fever, severe dementia, consciousness disturbance due to organic brain damages, need for emergency examination, hospital transfer or discharge or due to missing data on their amount of physical activity. As a result, a total of 421 patients comprised the analysis population [228 males, 193 females; mean age, 72.5±12.6 (S.D.) years; range 22-96 years]. The number of respondents for each question item is shown in Table 2.

Patients were initially examined for the presence of SAS (positive answer to Q7-a), RLS (positive answer to Q6-a), PLMD (positive answer to Q6-b or Q7-b) or NBD (positive answer to Q7-c). Those who were NOT diagnosed with SAS, RLS, PLMD or NBD were subsequently examined for the presence of insomnia. Patients were judged as having insomnia when the subjective sleep investigation indicated the presence of any one of the following:

i. Disturbances of initiating sleep (DIS): Q1, the answer indicates 30 min or more.
ii. Disturbances of maintaining sleep (DMS): Q2, the answer indicates three times or more.
iii. Early morning awakening (EMA): Q3, the answer indicates wake time 30 minutes or earlier than the desired time without falling asleep again.
iv. Non-restorative sleep (NRS): Q4, the answer indicates insufficient or poor sleep.

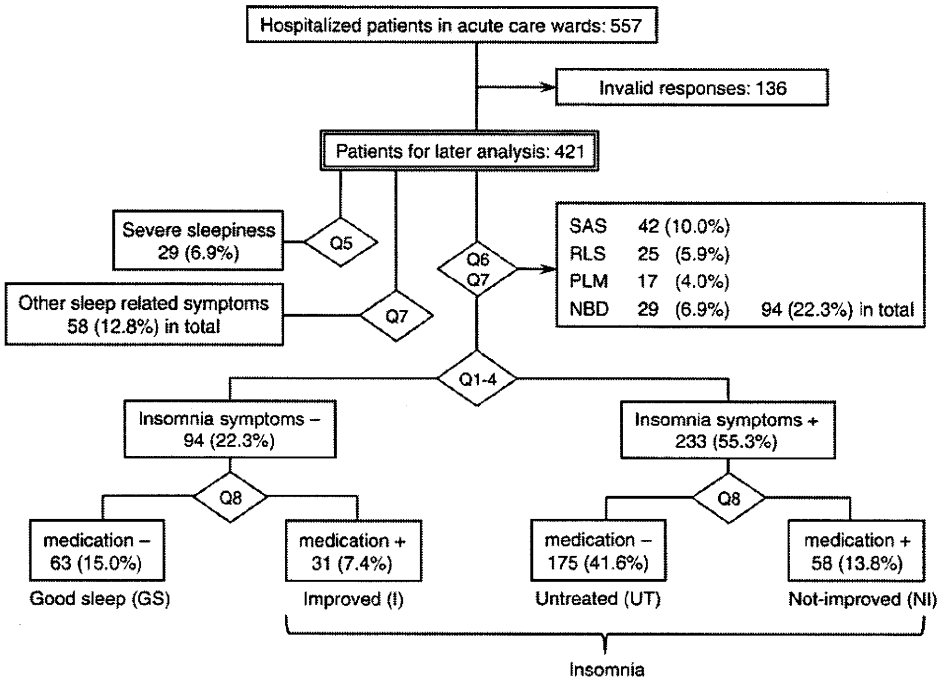

Fig. 1. Diagnostic flow of the subjects in this study. See text and Table 2 for explanation.

The subjects were also divided into the following four groups according to the presence or absence of insomnia and use or not of hypnotic-sedative drugs for insomnia treatment: the good sleep (GS) group consisting of those without insomnia and taking no medication, the improved (I) group consisting of those without insomnia and taking medication (s), the untreated (UT) group consisting of those with insomnia but taking no medication, and the not-improved (NI) group consisting of those with insomnia and taking medication(s). Of these groups, the I, UT and NI groups were grouped together and defined as the insomnia group (Fig. 1).

2.4. Daytime sleepiness

The 421 patients were examined for the presence or absence of daytime sleepiness according to the following criteria: Q5, the answer indicates the presence of moderate or severe sleepiness.

2.5. Sleep-related symptoms

The 421 patients were examined for the presence or absence of other sleep-related symptoms, such as hot flashes in the foot or body (Q6-c), night sweats (Q6-d), palpitations (Q6-e), anxiety and panic (Q6-f), sleep paralysis (Q6-g) and nightmares (Q6-h).

2.6. Statistical analysis

One-way analysis of variance followed by Tukey's multiple comparison tests was used to identify significant differences in sleep parameters (TST, TWT and SE) among the insomnia group and GS group. Sleep parameters were also compared between each sleep disorder group and the GS group using a two-tailed Student's t test. Analysis values are expressed as mean±S.D. Multiple logistic regression analysis was carried out to calculate the odds ratio (OR) and 95% confidence interval (CI) for assessing the association of primary disorders, sleep disorders and use of hypnotic-sedative drugs with severe sleepiness. Presence of severe sleepiness was used as the dependent variable, and primary disorders, sleep disorders and use of hypnotic-sedative drugs were used as independent variables. We performed multiple logistic regression analyses to control for all sociodemographic (sex and age) and other factors. Statistical significance was set at $P<.05$. All analyses were made using SPSS 11.5 for Windows.

3. Results

3.1. Prevalence of sleep disorders

The breakdown of the diagnoses of sleep disorders is shown in Fig. 1. Of the 421 inpatients, 42 (10.0%, M/F=29/13) had SAS, 25 (5.9%, 14/11) had RLS, 17 (4.0%, 11/6) had PLMD and 29 (6.9%, 19/10) had NBD. A total of 94 (22.3%) had at least one of the four sleep disorders. Seventeen patients had two sleep disorders concurrently.

Of the 421 inpatients, 58 (13.8%, NI) and 175 (41.6%, UT) complained of insomnia symptoms. A total of 264 (62.7%), including the NI, UT and I (31, 7.4%) groups were given a diagnosis of insomnia. The most common insomnia

Table 3
Comparison of objective sleep parameters determined by LC in the insomnia and good sleep patients

	SAS n=42	P	RLS n=25	P	PLMD n=17	P	NBD n=29	P	Insomnia						Good sleep n=63
									Untreated n=175	P	Improved n=31	P	Not-improved n=58	P	
TST (min)	367.6±119.2	.06	331.9±117.7	0	354.6±111.5	.01	359.8±126.1	.04	369.2±102.5	.04	400.7±118.4	n.s	399.7±91.0	n.s	409.4±102.4
TWT (min)	172.4±119.2	.05	208.1±117.7	0	185.4±111.5	.01	180.2±126.1	.04	170.3±102.3	.03	139.4±118.4	n.s	140.3±91.0	n.s	129.3±103.3
SE (%)	68.1±22.1	.05	61.5±21.8	0	65.7±20.6	.01	66.6±23.4	.04	68.4±19.0	.03	74.2±21.9	n.s	74.0±16.9	n.s	76.1±19.1

Value are expressed as mean±S.D..
P value vs. Good sleep group.
n.s; not significant.

symptom was DMS (60.1%), followed by DIS (41.2%), EMA (33.9%) and NRS (31.8%). Only 63 (15.0%) were free of the above-mentioned sleep disorders and were assigned to the GS group.

3.2. Objective sleep parameters

Sleep parameters in each sleep disorder group are summarized in Table 3. There were significant differences in TST [F(3,323)=3.24, P=.022], TWT [F(3,323)=3.28, P=.021] and SE [F(3,323)=3.31, P=.020) among the insomnia group and GS group. TST (P=.039) was significantly shorter and TWT (P=.033) and SE (P=.032) were significantly longer in the NI group than in the GS group. Patients with RLS (P<.01) and NBD (P<.05) also presented a significantly shorter TST, significantly longer TWT and significantly lower SE than those in the GS group. A similar tendency was observed for patients with SAS or PLMD (P<.06). On the other hand, we found no significant differences in the sleep parameters between the medicated group (the I or NI group) and the GS group, regardless of whether or not any subjective improvement was observed.

3.3. Daytime sleepiness

Of the 421 inpatients, 229 (54.4%) experienced moderate to severe sleepiness and 29 (6.9%) experienced severe sleepiness. Severe sleepiness was commonly observed in those with sleep disorders; it was most commonly observed in patients with multiple sleep disorders (27.8%, 5/18), followed by those with PLMD (18.2%, 2/11), SAS (17.9%, 5/28) and NBD (17.7%, 3/17). Multiple logistic regression analysis revealed that SAS (adjusted OR=3.78, 95% CI, 1.24–11.53, P<.05) and PLMD (adjusted OR=5.93, 95% CI, 1.50–23.4, P<.05) showed a significantly positive association with the presence of severe sleepiness.

3.4. Other sleep-related symptoms

Of the 421 inpatients, 19 (4.5%, M/F=7/12) had hot flashes, 29 (6.9%, 13/16) had night sweats, 5 (1.2%, 1/4) had palpitations, 4 (1.0%, 2/2) had anxiety or panic and 13 (3.1%, 7/6) had nightmares. None of the patients experienced sleep paralysis.

3.5. Prevalence of use of hypnotic-sedative drugs

Of the 421 inpatients, 116 (27.6%) were taking some kind of hypnotic-sedative drug for the treatment of insomnia symptoms. The breakdown of the prescribed drugs was as follows: benzodiazepine hypnotics including zolpidem and zopiclone accounted for 73.2% (26.1% for ultrashort-acting, 30.6% for short-acting and 16.5% for intermediate-acting), benzodiazepine anxiolytic accounted for 5.8%, antipsychotics accounted for 15.6% and other drugs accounted for 5.2% of all prescribed drugs. In the insomnia group, those receiving medication therapy for insomnia only accounted for 33.7% (the I+NI group). Two thirds of the patients receiving medication therapy (65.2%, corresponding to the NI group) complained of persistent insomnia symptoms. In addition, 36.0% of RLS patients, 29.4% of PLMD patients, 26.2% of SAS patients and 17.2% of NBD patients were taking at least one of the above hypnotic-sedative drugs.

4. Discussion

This is the first multicenter study investigating the prevalence of sleep disorders in inpatients of acute wards in general hospitals. Sleep disorders are extremely common disorders among community residents, and are even more so among patients with underlying physical diseases as in the subjects of the present study. Insomnia, as well as other sleep disorders, while frequently thought to be transitory or secondary to a physical disease, can become prolonged without appropriate treatment in the early stages. Furthermore, chronic sleep disorders can exacerbate lifestyle-related diseases such as hypertension and diabetes, and increase the risk of psychiatric symptoms such as depression and anxiety, not to cause subjective distress [16,17]. Many sleep disorders go undetected and are not appropriately treated in clinical practice. Therefore, this study was conducted to alert practitioners of sleep disorders to this situation, by shedding more light on their current status in general medical practice.

In the present study, we investigated the prevalence of sleep disorders and the use of hypnotic-sedative drugs in 421 inpatients with mean age of 72.5 years by questionnaire-, actigraph- and observation-based sleep evaluations, and have revealed a high prevalence of diverse types of sleep disorders