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.

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	SAS, RLS, PLMD and NBD	Insomnia			Good Sleep
	557 (100%)	94 (100%)	Improved 31 (100%)	Untreated 175 (100%)	Not-Improved 58 (100%)	63 (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.

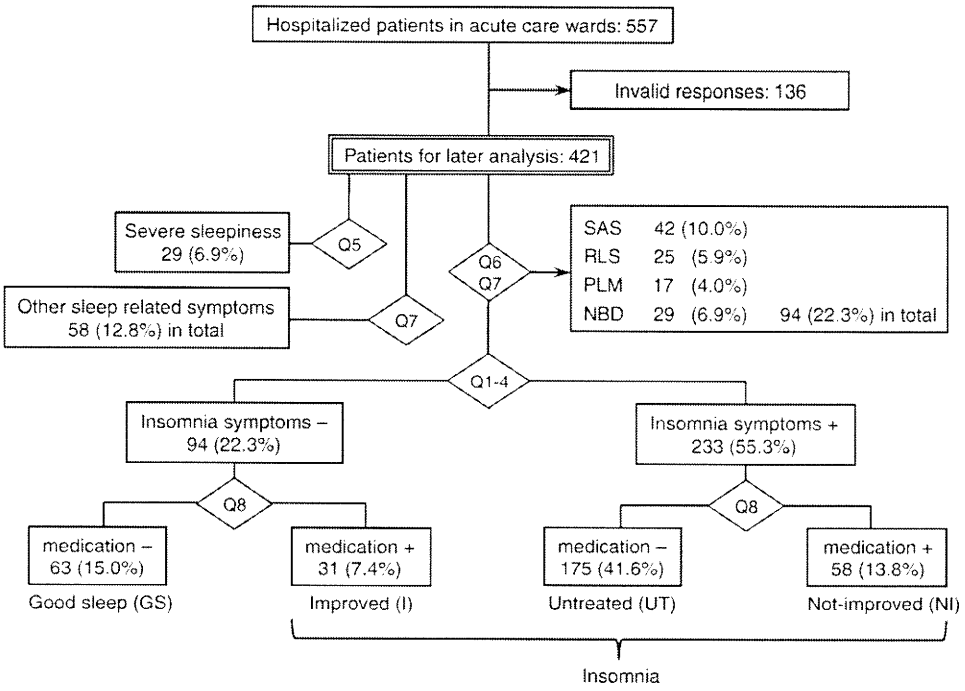

Fig. 1. Diagnostic flow of the subjects in this study. See text and Table 2 for explanation.

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

in the study population. SAS, RLS, PLMD, NBD and insomnia, in particular, were highly prevalent (10.0, 5.9, 4.0, 6.9 and 62.7%, respectively). The inpatients also suffered from various sleep-related symptoms (1.0–6.9%, except for sleep paralysis), which are common conditions with physical disorders and which could cause disrupted sleep [18–21]. In fact, the patients with these sleep disorders also showed poor sleep parameters recorded by actigraphy, which objectively indicates that they have poor-quality sleep during the night. Consequently, of the 421 patients, only 13.8% were free of any type of sleep disorder diagnosed, severe daytime sleepiness or sleep-related symptoms, revealing that sleep-related problems are very common clinical problems among inpatients of acute hospital wards.

Due to restrictions on the disclosure of personal information, the only information available regarding the underlying diseases of the patients was the names of the primary diseases according to the major classification of the *ICD-10*. We were thus unable to analyze respective medical conditions that are commonly associated with these sleep disorders, such as chronic pain, cardiovascular diseases, chronic renal failure, hemodialysis and iron deficiency anemia.

The prevalence of SAS and RLS is generally high in elderly people and patients with physical disorders. However, even though the mean age of our patients was high (72.5 years) and they had physical disorders in the exacerbation phase, contrary to our expectations, the prevalence of SAS and RLS was not higher in the study population than in community dwellers of previous studies. For example, the prevalence of SAS in middle-aged to elderly people has been shown to be 9–10% in males and 4–10% in females [22,23], which is comparable to that in the present study population (10% in the entire population, 12.7% in males, 6.7% in females). In the present study, patients were defined as having SAS if they reported loud snoring or apnea lasting for 10 seconds or more, because loud snoring is the most prominent symptom of upper airway resistance syndrome, which is included in the category of SAS [7,24]. Nevertheless, the prevalence of SAS patients including those who snored loudly in the present study was similar to that in the general population. Similarly, a large-scale survey which employed a self-administered questionnaire and used a definition of RLS similar to that in the present study has reported that the prevalence of RLS among Japanese people aged 70 years or more is 4.1% (3.4% in males, 4.6% in females), which is practically identical to that in the present study (5.9% in total, 6.1% in males, 5.7% in females) [25]. Furthermore, the frequency of NBD was as low as 6.9%, despite the occurrence rate of delirium per admission varying between 11 and 42% [26]. The low NBD frequency of the present study compared to that of all previous studies is thought to be because patients with severe physical conditions or with organic brain damages were excluded from the analyses.

In many of the epidemiologic studies on the prevalence of sleep disorders, sleep evaluation is performed during a period of one week to one month. The fact that sleep evaluation in this study was performed on a single night might have held down the prevalence of sleep disorders. However, since the physical status of the inpatients of acute hospital wards can change in a very short period of time and their sleep condition is also subject to change, we assumed that the results obtained from a long investigation period would not properly reflect the actual status of their sleep-related problems. Extension of the duration for determining the presence or absence of sleep disorders may result in a dramatic increase in the prevalence of the sleep disorders in inpatients of acute hospital wards.

Patients with physical disorders, especially with advanced age, are generally vulnerable to insomnia [27–29]. We have found that approximately two thirds (62.7%) of the representative patients in acute wards in Japan are suffering from insomnia. It was confirmed not only from the subjective complaints of patients but also from the objective sleep evaluation that the quality of sleep for patients with insomnia receiving no treatment or who had other sleep disorders was significantly lower than that for patients in the GS group (Table 3). A survey among 1500 community dwellers aged 55–84 years in the United States has demonstrated that the quality of sleep decreases in proportion to an increase in the number of physical disorders suffered [27]. Several studies have also reported a high prevalence (34–69%) of insomnia in outpatients of primary care clinics or regular inpatients with acute or chronic physical disorders [30–33]. The findings of the present study for acute ward inpatients are consistent with those obtained in the previous studies in spite of shorter-term sleep evaluation.

In many cases of sleep disorders, daytime sleepiness often occurs to compensate for low-quality sleep during the night. In the present study, 47.5% of the patients experienced mild or severer sleepiness and 6.9% experienced severe sleepiness, which was particularly high in those with multiple sleep disorders, including SAS, RLS, PLMD and NBD. The results of multiple logistic regression analysis indicated that severe sleepiness is significantly associated with SAS and PLMD, and not with an underlying disease or type of hypnotic-sedative drug.

Only one-third (33.7%) of the patients with insomnia included in the present investigation received treatment for insomnia symptoms. In addition, two-thirds (65.2%) of the patients receiving medication therapy complained of residual insomnia symptoms. The relatively low frequency of patients prescribed hypnotic-sedative drugs in the present study, which is very similar to that reported in the Meissner's study [30], suggests the possibility that physicians are not fully aware of the presence of insomnia in their patients.

The prescribed drugs mainly consisted of benzodiazepine hypnotics including intermediate-acting agents and antipsychotics. Caution should always be exercised when

using these hypnotic-sedative drugs in inpatients with physical disorders, especially in elderly patients. This is because elderly patients present a poor risk-benefit balance for hypnotic-sedative drugs due to such reasons as decreased drug metabolizing capacity, increased drug sensitivity, risk of fall and fracture or suppressed mental function, and worsening of underlying diseases induced by medication [34–37].

Moreover, administered hypnotic-sedative drugs may be ineffective or even worsen underlying diseases unless sleep disorders are properly diagnosed. In fact, 23.8% of the patients with SAS were prescribed hypnotic-sedative drugs including benzodiazepines and 36.0% of the patients with RLS were taking hypnotic-sedative drugs other than clonazepam. These results suggest that medications that are not necessarily appropriate for treatment of individual patients' sleep disorders are often selected in actual clinical practice, possibly causing a reduction in the patients' ADL and QOL.

Several limitations should be noted when interpreting the results of the present study. First, as elderly patients aged 65 years or more accounted for a large portion (76.0%) of the 421 inpatients, it is speculated that the high prevalence of sleep-related problems observed in the patients of the present investigation were associated with not only sleep disorders attributable to physical disorders but also age-related changes in sleep property.

Second, one-fourth (24.4%) of the initially enrolled 557 patients were excluded. Patients who were unable to answer questions on the day of the survey because of a change in their physical condition (e.g. fever, consciousness disturbance or need for emergency examination) or those patients with missing data due to interruptions in LC data collection were excluded. Some of these excluded patients might have developed some type of sleep disorder during their stay in hospital.

Third, insomnia defined in the present study is different from insomnia that meets the general criteria of the International Classification of Sleep Disorders, second edition (ICSD-2) [7], because we did not consider the presence or absence of "daytime impairment related to the nighttime sleep difficulty". This investigation item was not included in the present study because it was difficult to determine whether the patients' diverse psychosomatic symptoms observed during the daytime were attributable to insomnia or physical disorders.

Fourth, the questionnaire employed in the present study has not been validated. A set number of items taken from the original were configured so as to reduce the burden on inpatients who were in poor physical condition. Therefore, the questionnaire can only suggest the possibility of certain disorders such as SAS, PLMD and RLS; it does not predict the presence of these disorders with high accuracy. However, the frequency of sleep disorders and the percentage of patients exhibiting symptoms of insomnia found in the present study closely resemble the data of several other studies. This is thought to be indirect evidence that, to a certain degree, the survey items work effectively to detect patients suffering from sleep disorders.

Fifth, the sleep/wake scoring algorithm used for the LC data in the present study has been validated for a sample of healthy young subjects [15], but not for elderly subjects with physical disorders, as in the present study's sample. However, as the results demonstrate, meaningful differences were detected in the sleep parameters calculated with this algorithm for total sleep time, total wake time, and efficiency of sleep between the UT group with insomnia and the GS group. Given this, the clinical application of the LC and sleep/wake scoring algorithm for the subjects of the present study can be considered a sound approach to a certain degree.

5. Conclusion

In the present study, which initially involved 557 inpatients who had been admitted to acute hospital wards in 44 general hospitals, we have revealed an extremely high prevalence of sleep disorders using subjective and objective sleep evaluation scales, and have also indicated several problems in the current practice of sleep medicine. Proper diagnosis of sleep disorders should be made while being aware of the high prevalence of sleep disorders among elderly patients with physical disorders, and a treatment strategy that provides a favorable risk-benefit balance must be developed.

Acknowledgments

This study was supported by a Grant-in-Aid for Cooperative Research from the Ministry of Health, Labor, and Welfare of Japan (H19-kokoro-ippan-013, H20-tyojyu-ippan-001).

References

[1] Manabe K, Matsui T, Yamaya M, Sato-Nakagawa T, Okamura N, Arai H, et al. Sleep patterns and mortality among elderly patients in a geriatric hospital. Gerontology 2000;46:318–22.
[2] Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging: 1. Sleep disorders commonly found in older people. CMAJ 2007;176:1299–304.
[3] Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979;136:1257–62.
[4] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention. JAMA 1989;262:1479–84.
[5] Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R. An epidemiological study of insomnia among the Japanese general population. Sleep 2000;23:41–7.
[6] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6:97–111.

[7] American Acdemy of SleepMedicine. International classification of sleep disorders :Diagnostic and coding manual. 2nd ed. Westchester: Illinois; 2005.
[8] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
[9] Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998;97:2154–9.
[10] Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;9:251–7.
[11] Hui DS, Wong TY, Li TS, Ko FW, Choy DK, Szeto CC, et al. Prevalence of sleep disturbances in Chinese patients with end stage renal failure on maintenance hemodialysis. Med Sci Monit 2002;8:CR331–6.
[12] Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. J Clin Neurophysiol 2001;18:128–47.
[13] Nomura T, Inoue Y, Miyake M, Yasui K, Nakashima K. Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease. Mov Disord 2006;21:380–4.
[14] Hanly P, Powles P. Hypnotics should never be used in patients with sleep apnea. J Psychosom Res 1993;37(Suppl 1):59–65.
[15] Enomoto M, Eudo T, Suenaga K, Miura N, Nakano Y, Kohtoh S, et al. Newly developed waist actigraphy and its sleep/wake scoring algorithm. Sleep Biol Rhythms 2009;7:17–22.
[16] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217–39.
[17] Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. J Psychosom Res 2009;67:109–16.
[18] Ulloa EW, Salup R, Patterson SG, Jacobsen PB. Relationship between hot flashes and distress in men receiving androgen deprivation therapy for prostate cancer. Psychooncology 2009;18:598–605.
[19] Woodward S, Freedman RR. The thermoregulatory effects of menopausal hot flashes on sleep. Sleep 1994;17:497–501.
[20] Stein MB, Chartier M, Walker JR. Sleep in nondepressed patients with panic disorder: I. Systematic assessment of subjective sleep quality and sleep disturbance. Sleep 1993;16:724–6.
[21] Partinen M. Epidemiology of sleep disorders. In: Kryger M, Roth T, Dement W, editors. Principals and oractice of sleep medicine. 2nd ed. Philadelphia: WB Saunders; 1994. p. 437–52.
[22] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.
[23] Kim J, In K, You S, Kang K, Shim J, Lee S, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med 2004;170:1108–13.
[24] The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667–89.
[25] Enomoto M, Li L, Aritake S, Nagase Y, Kaji T, Tagaya K, et al. Restless legs syndrome and its correlation with other sleep problems in the general population of Japan. Sleep Biol Rhythms 2006;4:153–9.
[26] Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006;35:350–64.
[27] Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res 2004;56: 497–502.
[28] Stewart R, Besset A, Bebbington P, Brugha T, Lindesay J, Jenkins R, et al. Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. Sleep 2006;29: 1391–7.
[29] Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. Sleep 2007;30:213–8.
[30] Meissner HH, Riemer A, Santiago SM, Stein M, Goldman MD, Williams AJ. Failure of physician documentation of sleep complaints in hospitalized patients. West J Med 1998;169:146–9.
[31] Shochat T, Umphress J, Israel AG, Ancoli-Israel S. Insomnia in primary care patients. Sleep 1999;22(Suppl 2):S359–65.
[32] Terzano MG, Parrino L, Cirignotta F, Ferini-Strambi L, Gigli G, Rudelli G, et al. Studio Morfeo: insomnia in primary care, a survey conducted on the Italian population. Sleep Med 2004;5: 67–75.
[33] Aikens JE, Rouse ME. Help-seeking for insomnia among adult patients in primary care. J Am Board Fam Pract 2005;18:257–61.
[34] Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. Pharmacoepidemiol Drug Saf 2002;11:97–104.
[35] Mahoney JE, Webb MJ, Gray SL. Zolpidem prescribing and adverse drug reactions in hospitalized general medicine patients at a Veterans Affairs hospital. Am J Geriatr Pharmacother 2004;2:66–74.
[36] Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005;331:1169.
[37] Chang CM, Wu EC, Chang S, Lin KM. Benzodiazepine and risk of hip fractures in older people: a nested case-control study in Taiwan. Am J Geriatr Psychiatry 2008;16:686–92.