8

Encephalopathy Associated with Psychotropic Drug Therapy

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1. Introduction

All therapeutic interventions are double-edged swords with benefits and adverse effects, and pharmacotherapy is not an exception. Shortly after the introduction of conventional antipsychotic drugs into clinical practice, relatively rare but serious complications with hyperthermia, muscle rigidity, autonomic instability, and disturbed mental status were recognized to develop in some patients treated with antipsychotics. This type of encephalopathy induced by the use of antipsychotics was referred to as neuroleptic malignant syndrome (NMS), and almost all physicians prescribing antipsychotics are nowadays aware of this adverse phenomenon. Another well-known type of encephalopathy associated with psychotropic drug therapy is serotonin toxicity (ST) or serotonin syndrome (SS), which is characterized by autonomic and neuromuscular symptoms and altered mental status. In contrast with the idiosyncratic nature of NMS, ST is a spectrum pathophysiological state assumed to derive from excess serotonergic neural transmission caused by serotonin-related psychotropic agents. In these two decades, pharmacotherapy with psychotropic drugs for mentally ill patients has been dramatically changed, and classical prototypal antipsychotics and antidepressants have been replaced with atypical antipsychotics and selective serotonin reuptake inhibitors (SSRIs), respectively. These newly developed psychotropic drugs are generally safer and more tolerable than older drugs. However, atypical antipsychotics are not free of the risk of development of NMS, and the explosive prevalence of SSRIs prescribed not only for depression but also for a number of psychiatric diagnoses such as anxiety, eating, impulse-control, and personality disorders may increase the incidence of ST. Therefore, these two pathological states still remain as major adverse effects of psychotropic drugs involving altered functioning of the central nervous system (CNS), to which all clinicians prescribing psychoactive drugs should pay attention. The popularity of SSRIs also increased the case reports of patients suffering from discontinuation syndrome, which sometimes includes CNS symptoms like anxiety and irritability. In this chapter, the author provides a comprehensive overview of the above-mentioned adverse effects affecting the CNS function associated with psychotropic pharmacotherapy. In addition, several other pathological conditions potentially causing encephalopathic symptoms in psychiatric patients treated with psychotropic drugs, e.g., hyponatremia, valproate-induced hyperammonemia, transient splenial lesion of the corpus callosum, and so on, are also described.

2. Neuroleptic malignant syndrome

2.1 Historical background

In the late 1950s, immediately after the introduction of antipsychotics into the clinical practice, single case reports of encephalopathic reaction to antipsychotic agents with fever, muscle rigidity, and autonomic dysfunction were already described (Kinross-Wright, 1958; Preston, 1959). In 1960s, French psychiatrists took notice of such cases and designated them as NMS (Delay & Deniker, 1968). However, the syndrome had been thereafter reported only occasionally and little attention had been paid to the concept of NMS, especially in the United States, until Caroff (1980) reviewed 60 cases of NMS reported in the scientific literature to that time. His review article renewed interest of clinicians and researchers all over the world and proliferated the reports on the epidemiology, risk factors, symptomatology, diagnostic criteria, differential diagnoses, pathophysiology, and treatment of the syndrome. At the present time, NMS is one of the most popularly recognized complications of psychotropic pharmacotherapy and described in most standard medical textbooks.

2.2 Epidemiology

Along with an increase in awareness of its concept after the Caroff's review (1980), many patients diagnosed as NMS were reported throughout the world and it was recognized that NMS was not so rare than formerly supposed. In the review by Keck et al. (1991) on the epidemiology of NMS, the estimated frequency of NMS was reported to be within a wide range from 0.02 % to 2.4 %. The high incidence of NMS reported in earlier studies from the United States is, however, evidently overestimated due to a variety of factors, e.g., retrospective study design, loose diagnostic criteria, adherence to an amorphous "spectrum concept", and clinical practices in vogue (Adityanjee et al., 1999a). Based on the more recent reports (Spivak et al., 2000; Montoya et al., 2003; Shiloh et al., 2003) as well as my own clinical experience as a psychiatrist at the front for almost three decades, the incidence of definite NMS does not appear to exceed 2-3 cases out of one thousand consecutive patients treated with antipsychotics, as long as precautionary measures and monitoring are cautiously and sufficiently employed for the early recognition and prevention of NMS.

2.3 Clinical features

The principal clinical manifestations of NMS are characterized by the symptoms related to the following 4 major areas: (1) hyperpyrexia, (2) extrapyramidal symptoms (EPS), (3) altered mental status, and (4) autonomic instability. Hyperthermia is prerequisite to being diagnosed as NMS (Kurlan et al., 1984; Levenson, 1985; Addonizio et al., 1987; Caroff & Mann., 1988; Rosebush & Stewart, 1989), with a body temperature exceeding 38 ^{o}C in most cases, and as high as 40-41 ^{o}C in some patients. The EPS are also noted in almost all cases reported as NMS, typically represented as muscle rigidity accompanied by tremors, which is often described as "lead-pipe" or "plastic". Other forms of EPS including focal dystonia, sialorrhea, dysphagia, dysarthria, opisthotonus, oculogyric crisis, chorea and dyskinesia are sometimes observed as accompanying symptoms. Altered mental status includes varied levels of consciousness disturbances ranging from drowsiness to coma, confusion, agitation, delirium, stupor, mutism and so on. Involvement of the autonomic system is manifested by severe tachycardia, labile blood pressure, profuse diaphoresis, dyspnea and incontinence.

Although laboratory abnormalities of NMS are nonspecific, elevation of serum creatine phosphokinase (CPK) (>99 % derived from muscle fraction) is noted in almost all cases, which reflects significant muscle damage during development of NMS. In severely affected cases, it often exceeds 10,000 IU/liter with a high risk of development of myoglobinuria and renal failure. Leukocytosis is also seen in almost all patients with NMS. Hepatic enzymes are occasionally elevated but less dramatically than CPK.

Diagnosis of NMS is made based on the above-mentioned clinical symptoms and laboratory findings when these abnormalities develop subsequent to the initiation of or increase in antipsychotics and other medical conditions can be excluded. The typical cases with "full-blown" symptoms appear to be diagnosed with ease if the physician is aware of the concept of NMS. Several diagnostic criteria for NMS have been proposed by different researchers (Levenson, 1985; Addonizio et al., 1986; Pope et al., 1986; Adityanjee et al., 1988; J.H. Friedman et al., 1988; Keck et al., 1989a, 1989b; Caroff et al., 1991; Nierenberg et al., 1991; Caroff & Mann, 1993; Adityanjee et al., 1999b), and here presented in Table 1 is the research criteria for NMS described in DSM-IV-TR (Frances et al., 2000).

A.	The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.
B.	Two (or more) of the following: (1) diaphoresis (2) dysphagia (3) tremor (4) incontinence (5) changes in level of consciousness ranging from confusion to coma (6) mutism (7) tachycardia (8) elevated or labile blood pressure (9) leucocytosis (10) laboratory evidence of muscle injury (e.g., elevated CPK)
C.	The symptoms in Criteria A and B are not due to another substance (e.g., phencyclidine) or a neurological or other general medical condition (e.g., viral encephalitis).
D.	The symptoms in Criteria A and B are not better accounted for by a mental disorder (e.g., Mood Disorder With Catatonic Features).

Table 1. Research criteria for NMS described in DSM-IV (Frances et al., 2000)

2.4 Precipitating agents

Virtually all classes of dopamine D_2 receptor antagonists have been associated with NMS. This includes not only neuroleptics in a narrow sense (either typical or atypical antipsychotics) prescribed for the control of psychotic symptoms, but also several classes of drugs with the potential to block D_2 receptors in CNS used as antidepressants, antiemetics, anesthetics, and sedatives (e.g., Robinson et al, 1985; L.S. Friedman et al., 1987; Taylor & Schwartz, 1988; Madakasira, 1989; Spirt et al., 1992; Chan-Tack, 1999).

Aside from cases with NMS associated with the use of antagonists for dopamine D_2 receptors, the clinical features identical or closely resemblant to NMS have been occasionally reported to develop during the course of the treatment with antiparkinsonian drugs, especially after the withdrawal or reduction of them, in patients with Parkinson's disease (Henderson & Wooten, 1981; Toru et al., 1981; J.H. Friedman et al., 1985; Y. Yamawaki & Ogawa, 1992; Serrano-Dueňas, 2003; Takubo et al., 2003). In these cases, it may be inappropriate to use the term NMS since the patients were not receiving "neuroleptics" (Addonizio et al., 1987), and some strict researchers refer to such cases as "NMS-like state" (Toru et al., 1981), "malignant dopaminergic syndrome" (Serrano-Dueňas, 2003), or simply as "malignant syndrome" (Takubo et al., 2003). Irrespective of how it is called, the underlying pathophysiology to precipitate the clinical course in these patients is supposed to be dopaminergic hypofunction in CNS, which is identical to that in the patients with NMS induced by the use of antipsychotics. Therefore, it appears acceptable to consider the episode fulfilling the clinical features of NMS in patients with Parkinson's disease as a variant of NMS, even if it is not induced by the use of neuroleptics.

The similar syndromes have also been reported to be caused by numerous other classes of drugs with different mechanisms of action [e.g., lithium, clomipramine, nortryptiline, SSRIs, benzodiazepines] (Kellam, 1987a; Ananth et al., 2004a, but see also Assion et al., 1998), and even in the absence of any pharmacotherapeutic intervention (the so-called lethal catatonia), and thus some researchers have commented that NMS is a misnomer (Singh & Maguire, 1987; Brennan et al., 1988). They proposed novel names such as "iatrogenic malignant syndrome" (Singh & Maguire, 1987) or "pyrexial catatonia" (Kellam, 1987b) instead of NMS. Heyland & Sauvé (1991) suggested a new label "drug-induced central hyperthermic syndrome" for such cases. In my opinion, however, these designations are too vague as a diagnosis in clinical settings, and it should be avoided to broaden the concept of NMS to too much extent.

2.5 Risk factors

As shown in Table 2, there had been many potential risk factors for NMS identified or postulated in numerous reviews, case series, and reports published until 1989 (Keck et al., 1989a). Among them, demographic items such as sex, age, and psychiatric diagnosis are not of essential importance as risk factors (Caroff & Mann, 1993). It should be kept in mind that NMS can develop regardless of sex, age, and psychiatric diagnosis, when antipsychotic agents are administered to a patient. Case-controlled studies (Keck et al., 1989a; Berardi et al., 1998; Viejo et al., 2003) have indicated psychopathological features such as agitation, confusion, disorganized behavior, and catatonia, as well as pharmacological features such as higher neuroleptic dose at greater rates of dose increase and parenteral neuroleptic injections, as risk factors. It has been reported that antecedent existence of EPS including akathisia is also a risk factor of NMS (Berardi et al., 1998). NMS occurs independent of climate and ambient conditions (Caroff & Mann, 1993), and Viejo et al. (2003) were unable to find a significant difference in environmental temperature at onset of clinical symptoms of NMS between the cases and matched-controls. Considering various cases of NMS reported to develop during heat waves (Shalev et al., 1988; Fitzgerald et al., 1997), however, adverse climate conditions with high temperature and excessive humidity may be important in some cases to trigger the development of NMS. High serum CPK levels during psychotic episodes may also be a risk factor for NMS (Hermesh et al., 2002).

Demographic
Sex
Age
Psychiatric diagnosis
Medication-related
Maximum dose of neuroleptic
Rate of neuroleptic dose increase
Neuroleptic potency
Route of neuroleptic administration
Concurrent administration of lithium salts
Antecedent withdrawal of anticholinergic agents
Antecedent withdrawal of dopamine agonists
Medical status
Psychomotor agitation, exhaustion, or both
Antecedent or concurrent medical illness
Antecedent or concurrent neurological illness
Recent history of alcohol or other substance abuse or dependence
Thyrotoxicosis
Environmental
Elevated ambient temperature

Table 2. Risk factors for NMS identified or postulated until the report by Keck et al. (1989a)

Familial occurrence of NMS has been reported occasionally (Deuschl et al., 1987; Otani et al., 1991; Ziegenbein et al., 2006), suggesting that a predisposition to NMS is genetically governed in some cases. Extreme caution should be then paid to a patient with a family history of NMS, to whom it is necessary to initiate pharmacotherapy with antipsychotics.

2.6 Clinical course and outcome

Although the reported duration of exposure to antipsychotics prior to the development of NMS is extremely varied, the majority of cases occur within 1 to 2 weeks after the initiation of an offending drug (Shalev & Munitz, 1986; Addonizio et al., 1987; Caroff et al., 1988). Though nonspecific, the following signs and symptoms have been reported to precede NMS in some cases: unexpected changes in mental status, particularly obtundation or new-onset catatonia; episodic tachycardia, tachypnea, or hypertension; incontinence; low-grade temperature elevations; dysarthria, dysphagia, diaphoresis, sialorrhea, rigidity, myoclonus, tremor or other EPS unresponsive to antiparkinsonian agents; and unexplained elevation in serum CPK (Caroff et al., 1991; Caroff & Mann, 1993). Since almost all of these are themselves constituent symptoms of NMS (see above), it may be possible to diagnose a patient with such prodromal or early symptoms as NMS, depending on the diagnostic criteria of NMS adopted. At any rate, it is practically very important to be aware of sequential progression of symptoms of NMS in order to facilitate prompt recognition and interventions to abort the symptoms in its incipient stage. Analysis of the temporal sequence of the four predominant clinical features of NMS has indicated that either altered mental status or muscle rigidity precedes hyperthermia and autonomic dysfunction in the majority of fulminant NMS cases, most typically with the following order: (1) changes in mental status; (2) muscle rigidity; (3) hyperthermia; and (4) autonomic dysfunction (Velamoor et al.,

1994). Woodbery & Woodbery (1992) proposed five discrete stages toward the progression of NMS, from stage I or drug-induced parkinsonism to stage V (the severest form of fulminant NMS). This spectrum-based concept of NMS (Fig. 1) may be practically useful to comprehend the progression of symptoms, at least in typical cases (Odagaki, 2009).

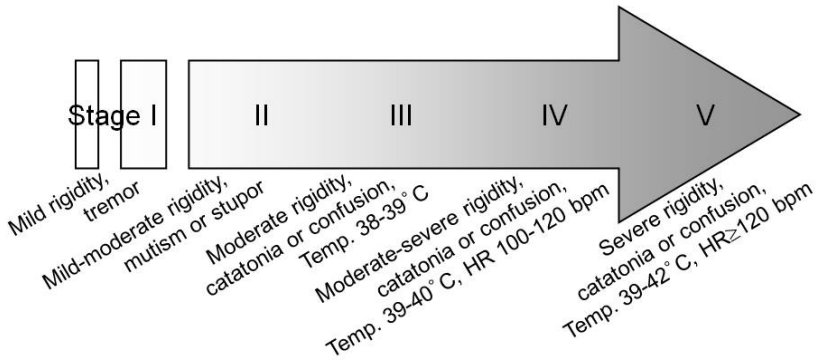

Fig. 1. The typical progression of symptoms of NMS from the mildest stage I (drug-induced parkinsonism) through stage V or the severest form of NMS (Odagaki, 2009). Stages I-V are originally proposed by Woodbury and Woodbury (1992) and adapted by Strawn et al. (2007).

Once antipsychotics are stopped, NMS is self-limited barring complications, with the duration to resolution of NMS up to two weeks in the majority of cases (Shalev & Munitz, 1986; Addonizio et al., 1987; Caroff et al., 1988). The notion that prompt withdrawal of the offending agent at early stage can prevent progression to definite NMS has been corroborated by the study reported by Shiloh et al. (2003).

The clinical course of NMS can be modified by concurrence of many complications. Although most medical problems are reported as complications (Addonizio et al., 1987), one of the most common and serious complications of NMS is acute renal failure caused by rhabdomyolysis (Levenson, 1985). As it has been reported that renal failure and myoglobinemia are associated with a significantly higher risk of mortality in NMS (Shalev et al., 1989), careful monitoring is necessary as to serum CPK levels, myoglobinemia /myoglobinuria, and renal functions throughout the course of NMS. As impressed with its designation, NMS is potentially lethal (Kellam, 1987a). The mortality rate was, however, reported even in the late 1980s to be apparently declined as compared with the former reports, and the overall rate of mortality for patients without concurrent organic diseases was reported as less than 10 % since 1984 (Shalev et al., 1989). The survey on NMS cases conducted in Japan also showed a clear chronological decline of mortality rate, which reached below 10 % in the latest years of the survey (S. Yamawaki et al., 1990).

Although persistent, long-term clinical sequelae of NMS were historically considered rare, there have been substantial case reports with deficits related to complications or severity of the syndrome, particularly hypoxia or hyperthermia. As neuropsychiatric sequelae of NMS, Adityanjee et al. (2005) raised CNS dysfunctions manifested as cognitive impairment or as

parkinsonian syndrome, peripheral neurologic impairment such as peripheral neuropathy, and psychological impairment including severe depression.

2.7 Differential diagnosis

Differential diagnosis is of prime importance, because NMS constituted with nonspecific symptoms and laboratory abnormalities is a diagnosis of exclusion. The disorders listed in Table 3 (Strawn et al., 2007) should be considered as differential diagnoses.

Infectious
Meningitis or encephalitis
Postinfectious encephalomyelitis syndrome
Brain abscess
Sepsis
Psychiatric or neurological
Idiopathic malignant catatonia
Agitated delirium
Benign extrapyramidal side effects
Nonconvulsive status epileptics
Structural lesions, particularly involving the midbrain
Toxic or pharmacological
Anticholinergic delirium
Salicylate poisoning
Malignant hyperthermia (inhalational anesthetics, succinylcholine)
Serotonin syndrome (monoamine oxidase inhibitors, triptans, linezolid)
Substances of abuse (amphetamines, hallucinogens)
Withdrawal from dopamine agonists, baclofen, sedative-hypnotics, and alcohol
Endocrine
Thyrotoxicosis
Pheochromocytoma
Environmental
Heatstroke

Table 3. Differential diagnosis of NMS (Strawn et al., 2007)

Among these, idiopathic malignant (lethal) catatonia and SS are of special importance from the practical as well as theoretical viewpoints. Idiopathic malignant catatonia, a life-threatening febrile neuropsychiatric syndrome that had been described well several decades before the advent of antipsychotic drugs, is clinically quite similar to, and often indistinguishable from, NMS (Mann et al., 1986). Some researchers indeed regard NMS as a drug-induced iatrogenic form of malignant catatonia with the same underlying pathophysiology (Mann et al., 1986; White, 1992; Fink, 1996a; Carroll & Taylor, 1997; Fricchione et al., 2000). On the other hand, Castillo et al. (1989) emphasized the importance of differentiating these two syndromes clinically. In response to the editorial by Fink (1996a), Northhoff (1996) also contributed a correspondence against the notion that NMS and catatonia were variants of the same disorder. The similar debate has been held on the discrimination between NMS and SS (Fink, 1996b; Kontaxakis et al., 2003; Odagaki, 2009; Steele et al., 2011). It is beyond the scope of this article to have a detailed discussion on the

possibility that NMS belongs to a spectrum of the same disorder that contains catatonia and/or SS. Nevertheless, clinicians should keep an effort to differentiate NMS from other pathological conditions as long as there may be some differences in etiology, pathophysiology, and treatment.

2.8 NMS associated with atypical antipsychotics

With widespread use of atypical antipsychotics in recent years, NMS induced by these drugs has attracted much attention of clinicians and researchers (Caroff et al., 2000; Farver, 2003; Ananth et al., 2004b; Trollor et al., 2009). At the same time, great interest has also been taken in the concept of "atypical NMS", which is often presumed to be more associated with atypical antipsychotics than with conventional drugs (Picard et al., 2008). Though still controversial, the review of Trollor et al. (2009) suggests that NMS associated with atypical antipsychotics manifests in a typical manner, with one notable exception of clozapine-induced NMS which appears to be less associated with EPS. It should be borne in mind that even the atypical antipsychotics have the potential to precipitate the patient to NMS, as long as they are dopamine D_2 receptor antagonists.

2.9 Pathophysiology

Although the precise pathophysiological mechanisms underlying NMS are still unknown, antipsychotic-induced dopamine D_2 receptor blockade in the striatum and hypothalamus likely plays a pivotal role, at least at its initial stages, for the development of NMS (Mann et al., 2000). In addition to dopaminergic dysfunction, complex alterations in functioning of different neurotransmitters in various brain regions, e.g., norepinephrine, serotonin, γ-aminobutyric acid (GABA), and glutamate, are believed to be involved in the expression of multifarious clinical features of NMS (Ananth, 2004a). Through complex neurochemical as well as structural interactions among multiple neural transmission systems, a vicious circle likely develops to end a failure of homeostasis, irreversibly and lethal in some cases, that is involved in maintenance of consciousness and regulation of extrapyramidal motor function, body temperature, and autonomic functions. Especially in the fulminant cases with severe autonomic instability, uncoordinated hyperactivity of the peripheral sympathoadrenal systems, culminating in an end-stage hypermetabolic syndrome, is hypothesized (Feibel & Schiffer, 1981; Gurrera & Romero, 1992; Gurrera, 1999).

2.10 Treatment

One of the most important, and probably the most effective measures to avoid "malignant" sequence of the syndrome is a removal of the potentially offending drug(s) as prompt as possible. Although the treatment of NMS should be individualized for each patient depending on the clinical features and situations, the mainstay is good supportive medical care against extreme hyperthermia, dehydration, metabolic acidosis, nutritive and electrolyte imbalance, and occurrence of the complications including cardiorespiratory and/or renal failures, aspiration pneumonia, rhabdomyolysis, and coagulapathies. Several specific treatments recommended for management of NMS (Table 4) should be taken into consideration as additional therapeutic options, based on the severity and clinical course (Sakkas et al., 1991a, 1991b; Davis et al., 2000). However, it should be stressed that these

specific remedies for NMS are derived from empirical reports or theoretical grounds, rather than based on prospective, randomized controlled studies (Susman, 2001). For instance, conflicting results have been shown even about the usefulness of dantrolene and bromocriptine, the two most well established drugs for treatment of NMS (Rosenberg & Green, 1989; Rosebush et al., 1991; Reulbach et al., 2007).

Treatment with	Comments
Anticholinergics	Still controversial, but may be useful in mild or early cases to help attenuate EPS (Woodbury and Woodbury, 1992)
Benzodiazepines	May be useful when catatonic symptoms predominate (Francis et al., 2000)
Dopaminergic agonists	
Bromocriptine	One of the most well established pharmacologic agents for NMS (Rosenberg & Green, 1989; Sakkas et al., 1991a, 1991b)
Levodopa	Successful cases reported (Harris et al., 1987; Sakkas et al., 1991a; Nisijima et al., 1997)
Amantadine	Its use associated with a statistically significant decrease in mortality (Sakkas et al., 1991a, 1991b)
Dantrolene	One of the most well established pharmacologic agents for NMS (Rosenberg & Green, 1989; Sakkas et al., 1991a, 1991b)
Electroconvulsive therapy (ECT)	Should be considered when pharmacotherapy has failed or when idiopathic malignant catatonia cannot be ruled out (Davis et al., 1991; Trollor & Sachdev, 1999)

Table 4. Specific therapeutic remedies proposed for treatment of NMS

3. Serotonin toxicity (serotonin syndrome)

3.1 Historical background

The term "serotonin syndrome (SS)" was originally derived from the experimental behavioral model in rodents (Jacobs, 1976; Gerson & Baldessarini, 1980), and introduced into clinical medicine in 1982 for the first time to describe the toxic reactions to the co-administration of a monoamine oxidase inhibitor (MAOI) clorgyline and a tricyclic antidepressant (TCA) clomipramine in two obsessive-compulsive disorder patients (Insel et al., 1982). In fact, however, many similar case reports date back to 1950s (e.g., Mitchell, 1955), the era of prevailing use of MAOIs such as isoniazid and iproniazid as antidepressants or antituberculous drugs (Gillman, 1998). The first review article on SS, based on the summary of 12 clinical reports between 1982 and 1990 (Sternbach, 1991), was instrumental in popularizing the syndrome to physicians, and awareness of SS as a distinct clinical entity increased the number of reported cases diagnosed as SS in the following two decades.

As pointed out by Isbister & Buckley (2005), the term SS is often equivocally used and the clinical literature on this subject is sometimes inconsistent and confused. In the present article, the term "serotonin toxicity (ST)" is generally used to refer to the clinical state with any signs or symptoms reasonably attributable to excess serotonin caused by serotonergic agents.

3.2 Clinical features and diagnosis

According to the conventional definition based on relatively severe cases reported in the literature (Sternbach, 1991), SS can be described as a clinical triad of (1) mental-status changes, (2) autonomic hyperactivity, and (3) neuromuscular abnormalities. The diagnostic criteria for SS suggested by Sternbach (1991) are shown in Table 5.

A.	Coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features are present: 1) mental status changes (confusion, hypomania) 2) agitation 3) myoclonus 4) hyperreflexia 5) diaphoresis 6) shivering 7) tremor 8) diarrhea 9) incoordination 10) fever
B.	Other etiologies (e.g., infectious, metabolic, substance abuse or withdrawal) have been ruled out.
C.	A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.

Table 5. Suggested diagnostic criteria for SS (Sternbach, 1991)

In practice, the signs and symptoms of ST range from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and excessive hyperthermia in life-threatening cases, depending on the extent of serotonin excess. The clinical sequelae of serotonin excess are best thought of as a spectrum of toxicity, rather than a defined clinical entity (syndrome) with clear prognostic importance (Dunkley et al., 2003). Randomski et al. (2000) divided the cases into: (1) mild state of serotonin-related symptoms; (2) serotonin syndrome (full-blown form); and (3) toxic states (Fig. 2).

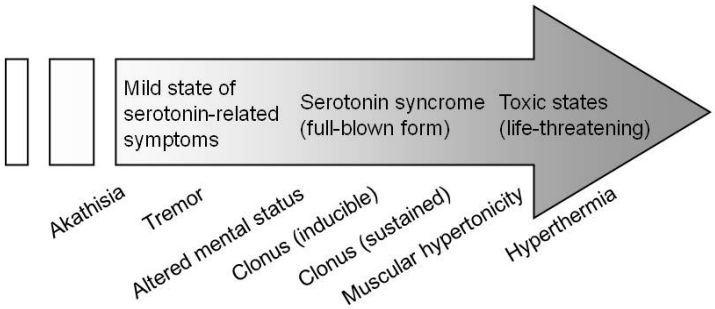

Fig. 2. Spectrum concept of ST (Adapted from Boyer & Shannon, 2005), with three clinical stages designated by Radomski et al. (2000).

To assess the severity of ST, the scale developed by Hegerl et al. (1998) may be useful. When adapted to the depressed patients treated with paroxetine, it was positively correlated with paroxetine concentrations and inversely correlated with auditory evoked potential (an indirect measure of serotonergic activity). Their scale consists of the following nine items each rated from 0 to 3: agitation, disorders of orientation, myoclonus, hyperreflexia, tremor, dizziness, hyperthermia, sweating, and diarrhoea.

Dunkley et al. (2003) analyzed the clinical data in 2222 consecutive cases of self-poisoning with serotonergic drugs, and found that several clinical features were associated with the diagnosis of SS. They developed the diagnostic decision rules for ST (Fig. 3), based on the results of their analysis as well as by including muscular hypertonicity and hyperthermia, both characteristic symptoms of the severe, life-threatening SS cases.

The onset of symptoms is usually rapid, with clinical findings often occurring within minutes, and in most cases within 24 hours, after initial use, an overdose, or a change in dosing of the offending drug(s) (Mason et al., 2000). It should be noted that the syndrome is often misdiagnosed initially, especially as exacerbation of psychiatric disorder with anxiety or agitation (MacKay et al., 1999; Attar-Herzerg et al., 2009). Patients with mild manifestations may present with subacute or chronic symptoms, whereas severe cases may progress rapidly to death (Sporer, 1995; Boyer & Shannon, 2005). The most notorious example of such fatal patients is the 'Libby Zion' case (Asch & Parker, 1988). Other severe complications of SS include seizures, disseminated intravascular coagulation, respiratory failure, severe hyperthermia, ventricular arrhythmia, and rhabdomyolysis (Sporer, 1995). Milder cases show resolution of the symptoms typically within 24 hours once the offending agents are discontinued (Sternbach, 1991).

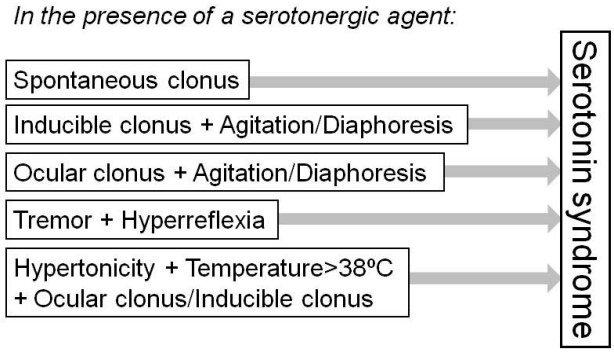

Fig. 3. Diagnostic criteria for SS proposed by Dunkley et al. (2003).

There are no confirmatory or specific laboratory tests available for the diagnosis of SS. Laboratory tests are best used to identify potential complications and assist in overall patient care. Elevated CPK has been reported in 18 % (Mills, 1997) or 34 % (Keck & Arnold, 2000) of the cases, usually associated with muscle rigidity and rhabdomyolysis. Electroencephalograms (EEG) may show general slowing, consistent with diffuse encephalopathy (Mills, 1997). Highly abnormal EEG findings, such as (poly-)spikes and waves (Lejoyeux et al., 1992) and pronounced triphasic waves (Dike, 1997), were also reported in patients with SS.

3.3 Precipitating agents

Virtually all medications that potentiate serononergic neurotransmission in the CNS have been reported in association with the cases of SS (Keck & Arnold, 2000), either alone or in combination. As shown in Table 6, the most common drug combinations causing the SS are MAOIs and antidepressants (SSRIs or TCAs) (Sporer, 1995). The severity of ST precipitated by the offending drug(s) is predictable well according to the serotonin levels measured in animal experiments (Gillman, 2006). The highest serotonin levels determined by microdialysis studies is achieved by the combination of MAOI and serotonin reuptake inhibitor (SRI) (100-fold as compared with baseline), followed by MAOI plus L-tryptophan (15-fold), MAOI alone (10-fold), moclobemide plus 3,4-methylenedioxymethamphetamine (MDMA) (10-fold), MDMA alone (5-fold), SSRI alone (3-fold), venlafaxine alone (3-fold), moclobemide alone (1.5-fold), TCA alone (1.25-fold), and mirtazapine alone (1.2-fold). Although mirtazapine alone stands at the lowest risk for ST, there has been a case report of severe SS induced by mirtazapine monotherapy (Hernández et al., 2002).

Drug combination	Number of cases
MAOI + Pethidine (Meperidine)	9
MAOI + Dextromethorphan	4
MAOI + Tryptophan	9
Reversible MAOI + TCA	2
Reversible MAOI + SSRI	5
MAOI-B + SSRI	6
MAOI-B + TCA	2
MAOI + SSRI	24
MAOI + TCA	16
SSRI + Dextromethorphan	1
SSRI + Tryptophan	5
SSRI + Lithium	1
SSRI + Pentazocine	1
Buspirone + Trazodone	1
TCA + Lithium	1
Bromocriptine + Levodopa	1
Phenelzine + Trazodone + Dextropropoxyphene	1
Clomipramine	1
MDMA	2
Fentanyl + Sertraline	1
Sertraline	1
Ademetionine (*S*-Adenosyl methionine) + Clomipramine	1

Table 6. List of the agents reported to cause SS (Sporer, 1995)

3.4 Differential diagnosis

The differential diagnosis of SS involves disorders producing cognitive and behavioral, neuromuscular, and autonomic nervous system dysfunction with or without hyperthermia (Keck & Arnold, 2000), such as anticholinergic poisoning, malignant hyperthermia, and NMS (Boyer & Shannon, 2005). SS can be confused with NMS, particularly when both

serotonergic and neuroleptic drugs had been used concomitantly in a patient showing severe life-threatening symptoms and/or complications described before. The following features are raised by Gillman (1999) for differentiation between the two syndromes: NMS, slow onset (days to weeks) and slow progression over 24-72 hours in association with neuroleptics versus SS, both rapid onset and rapid progression (minutes to hours) in association with a combination of serotonergic drugs; NMS, bradykinesia and lead pipe rigidity versus SS, hyperkinesias and clonus; and NMS, an idiosyncratic reaction to therapeutic dosages versus SS, a manifestation of toxicity (usually to a combination of drugs) to which everyone is liable. The differential diagnosis between SS and NMS can be further complicated when atypical antipsychotics are included in the prescription, because some of atypical antipsychotics are 5-HT_{1A} receptor agonist by themselves (Odagaki, 2009).

3.5 Pathophysiology

It has been well accepted that excess serotonergic signal transduction in CNS, resulting mostly from increase in serotonin concentrations by several mechanisms, explains most, if not all, of the clinical features of ST or SS. However, it should be noticed that much of our understanding of the pathophysiology of SS derives from preclinical data. As indicated by Isbister & Buckley (2005), there is no evidence that serotonin behavioral syndrome defined in experimental behavioral pharmacology and ST/SS described in clinical medicine are even similar in terms of phenomenology or underlying mechanisms. The significant confusion in the literature has been created especially as to the pathophysiological roles of 5-HT_{1A} and 5-HT_{2A} receptors implicated in SS. As discussed earlier (Isbister & Buckley, 2005; Odagaki, 2009), the possible important roles of 5-HT_{2A} receptors in pathogenesis of SS, in particular the severe cases with hyperthermia and/or muscle hypertonicity, should be taken into consideration.

3.6 Treatment

Of most importance are prompt recognition of toxicity and discontinuation of offending medications in management of ST. Most cases of ST, even if represented as a full-blown form of SS, are self-limiting, if medications are withdrawn promptly at their early stages and no complications occur. In some patients, however, life-threatening severe toxicity can develop. Severe toxicity is more likely in patients ingesting overdosed serotonergic agent(s) or at least two drugs with different mechanisms of action, with combinations of SSRIs and a MAOI being the most common (Isbister & Buckley, 2005). The Toxic Exposure Surveillance System in the United States reported over 100 deaths related to ingestion of SSRIs in 2004 (Watson et al., 2005), though it was unclear whether all of these cases could be diagnosed clinically as SS.

Most cases with ST can be managed by means of supportive care with intravenous fluids as well as with symptomatic therapies according to the clinical features and severity, e.g., aggressive external cooling for hyperthermia, benzodiazepines or barbiturates for seizures, and benzodiazepines for muscle rigidity, myoclonus, or agitation. The use of nondepolarizing paralyzing agents under mechanical ventilation is indicated when muscle rigidity remains refractory to benzodiazepines (Mills, 1995; Isbister & Buckley, 2005).

In the severe SS cases, more specific therapy may be considered. The most commonly used drugs have been methysergide, cyproheptadine, and chlorpromazine (Mills, 1995; Gillman, 1999). However, the SS cases reported to be successfully treated with these medications are all anecdotal, with randomized controlled trials lacking. Based on the pharmacological properties of these drugs as well as on the experimental results using an animal model of SS (Nisijima et al., 2007), Isbister & Buckley (2005) suggested that nonselective 5-HT_2 antagonists such as ketanserin or selective 5-HT_{2A} antagonists such as atypical antipsychotics may be effective for the treatment of SS. The use of atypical antipsychotics for treating SS is, however, not recommended, at least when NMS is not clearly excluded. There has been a report of the patient who showed SS caused by sertraline intake and consecutively NMS induced by risperidone (J.-M. Kim et al., 2007).

4. SSRI discontinuation syndrome

4.1 Background

Pharmacotherapy for mood and anxiety disorders has been dramatically changed during the last two decades, especially with an expanding increase in use of SSRIs for the treatment of broad spectrum including depression, varied types of anxiety, eating, obsessive-compulsive, and impulse-control disorders. In parallel with the wide-spread use of SSRIs, reports of SSRI discontinuation syndrome have been increased. As described below, it sometimes involves alterations in mental function, which may be interpreted as a relapse or worsening of the original disorders. This is the reason why the author intends to summarize the syndrome in brief here in this chapter.

Antidepressant discontinuation syndrome (Dilsaver & Greden, 1984; Dilsaver et al., 1987; Lejoyeux et al., 1996) had been well identified since first reported for imipramine in 1959 (Andersen & Kristiansen, 1959; Mann & MacPherson, 1959, as cited in these three reviews). The initial SSRI discontinuation syndrome was described for fluoxetine in 1988 (Cooper, 1988), and subsequent many case reports and review articles indicated it can develop for all SSRIs. Some researchers include discontinuation symptoms related with other antidepressants than SSRIs, such as venlafaxine, nefazodone, trazodone, and mirtazapine, in the same syndrome (Schatzberg et al., 1997a; Tamam & Ozpoyraz, 2002).

Although the terms *discontinuation* and *withdrawal* are sometimes used interchangeably, the latter should be avoided for the patients treated with antidepressants including SSRIs, since these drugs are, unlike opiates or sedative-hypnotics, non-addictive (Schatzberg et al., 1997b; Shelton, 2006).

4.2 Clinical features and diagnosis

Schatzberg et al. (1997b) raised the hallmark features of SRI discontinuation syndrome, as shown in Table 7. The clinical symptoms of SSRI discontinuation syndrome resemble those of TCA discontinuation syndrome, which had been classified into the following five main categories (Dilsaver & Greden, 1984; Dilsaver et al., 1987; Lejoyeux et al., 1996; Haddad, 1997; Taman & Ozpoyraz, 2002): (1) gastrointestinal and general somatic distress symptoms, e.g., anxiety, agitation, muscle tension, nervousness, flu-like symptoms (fatigue, headache, sweating, myalgia), lethargy, nausea, vomiting, asthenia; (2) sleep disturbances, such as insomnia and excessive and vivid dreams, (3) movement disorders, e.g., akathisia,

parkinsonism, unsteady gait, abnormal movements of mouth and tongue; (4) behavioral activation, such as panic attacks, delirium, mania or hypomania; and (5) miscellaneous symptoms, such as cardiac arrhythmias. In the case of SSRI discontinuation syndrome, however, cardiac arrhythmias are seldom or never observed (Haddad, 1998), probably due to their minimal or negligible antimuscarinic activity and cardiotoxicity. In addition to, and probably overlapped with, these symptoms commonly seen in TCA discontinuation syndrome, further three symptom clusters are described to follow SSRI termination, i.e., (1) problems with balance (dizziness, ataxia, vertigo); (2) sensory abnormalities (electric shock-like sensations, paresthesia); and (3) aggressive and impulsive behavior (suicide attempts, hoarding during discontinuation) (Haddad, 1998). The proposed diagnostic criteria (Black et al., 2000) are shown in Table 8.

Hall mark features of SRI discontinuation syndrome	
1.	Not attributable to other causes
2.	Emergent upon abrupt discontinuation, intermittent noncompliance (e.g., missed doses, drug holidays), and less frequently, with dose reduction
3.	Generally mild and short-lived
4.	Self-limiting but can be distressing
5.	Rapidly reversed by the reintroduction of the original medication or the substitution of one that is pharmacologically similar
6.	Minimized by slow tapering or by using a drug with an extended half-life

Table 7. Hall mark features of SRI discontinuation syndrome (Schatzberg et al., 1997b)

Criterion	Description
A	Discontinuation of or reduction in dose of an SSRI after a period of use of at least 1 month
B	Two (or more) of the following, developing within 1 to 7 days of criterion A Dizziness, light-headedness, vertigo or feeling faint Shock-like sensations or paresthesia Anxiety Diarrhea Fatigue Gait instability Headache Insomnia Irritability Nausea and/or emesis Tremor Visual disturbances
C	The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational or important areas of functioning
D	The symptoms are not due to a general medical condition and are not better accounted for by recurrence of symptoms of the mental disorder for which the SSRI was originally prescribed, or by concurrent discontinuation (or reduction in use) of another psychoactive substance

Table 8. The proposed diagnostic criteria for SSRI discontinuation syndrome (Black et al., 2000)

SSRI discontinuation symptoms occur within 1 to 3 days subsequent to cessation of treatment or reduction in dose in the majority of cases (Black et al., 2000). In the case of fluoxetine, however, the symptoms can develop slower (Einbinder, 1995) due to its longer half-life compared with those of other SSRIs (Table 9). In most cases, the syndrome is mild and short-lived, with persisting duration usually not exceeding 1-3 weeks even if untreated (Coupland et al., 1996; Black et al., 2000).

SSRI	Half-life (Haddad, 1998)		Half-life
	Single dose	Multiple dose	(Schatzberg et al., 1997a)
Paroxetine	10 h	21 h	21 h
Fluvoxamine	15 h	22 h	15 h
Sertraline	26 h	26 h	26 h (66 h)*
Citalopram	33 h	33 h	
Fluoxetine	1.9 d	5.7d (7-15d)*	84 h (4-16 d)*

*Half-life for an active metabolite shown in parentheses. h=hours, d=days.

Table 9. Half-lives of SSRIs (Schatzberg et al., 1997a; Haddad, 1998)

The half-life of the SSRI and its active metabolite (Table 9) probably contributes also to the likelihood of developing discontinuation syndrome for each drug. As anticipated from the half-life, the discontinuation events are more frequently and profoundly experienced with SSRIs with shorter half-life, in particular with paroxetine, and least often with fluoxetine that has the longest half-life (Coupland et al., 1996; Price et al., 1996; Rosenbaum et al., 1998).

4.3 Pathophysiology

As indicated above, plasma half-life of the SSRI is apparently one of the most important factors for occurrence of discontinuation syndrome, and thus the pathogenic mechanisms underlying SSRI discontinuation syndrome have to be supposed in accordance with this fact. The simplest and most plausible explanation is an abrupt decrease in availability of synaptic serotonin caused by withdrawal or decrease of the SSRI, in the face of down-regulated serotonin receptors as a result of synaptic adaptation to long-term SSRI treatment (Schatzberg et al., 1997a).

In addition to this hypothesis, Schatzberg et al. (1997a) also raised the following three other mechanisms that possibly contribute to some clinical features of the syndrome: (1) secondary effects on other neurotransmitters than serotonin; (2) individual genetic or psychological differences; and (3) cholinergic rebound.

4.4 Clinical implications and treatment

Rosenbaum & Zajecka (1997) indicated practical strategies for management of SRI discontinuation syndrome as follows: (1) reassuring patients that the symptoms are likely to be short-lived and mild; (2) for severe and distressing symptoms, the dosage of the drug prescribed immediately before the onset of discontinuation symptoms should be reinstituted and the rate of taper should be slowed; (3) all SRIs, with the exception of fluoxetine, should be gradually tapered; and (4) using or switching to agents with an extended half-life, such as fluoxetine, can help reduce the incidence of SRI discontinuation syndrome.

The rate of tapering of the drug should depend on its pharmacokinetic and pharmacological profile, current dose, duration of treatment, other drugs concomitantly prescribed, the patient's physical, psychological, and social situations, and so on. Physicians who prescribe SSRIs should be aware of the risk of this syndrome at the termination of treatment, or even during maintenance therapy with a fixed dose. Missing even as few as two doses of a SSRI with a short half-life, which is very often unreported to the physician, might lead to the discontinuation symptoms (Kaplan, 1997). It should be noted some discontinuation symptoms, e.g., anxiety, irritability, fatigue, and insomnia, are sometimes hardly distinguishable from those of a relapse or recurrence of the primary affective or anxiety disorders.

5. Other encephalopathic symptoms associated with psychotropic drugs

5.1 Hyponatremic encephalopathy

Hyponatremia is among the most common electrolyte abnormalities encountered in clinical practice (Upadhyay et al., 2006, 2009), and it is not rare to experience encephalopathic symptoms such as seizures and altered consciousness due to severe hyponatremia, usually in association with psychogenic polydipsia (Dundas et al., 2007) or self-induced water intoxication (Vieweg et al., 1987; Riggs et al., 1991), in psychiatric patients treated with psychotropic drugs (de Leon et al., 1994).

Clinical severity of hyponatremia is related not only to the absolute level of serum sodium concentration, but also to the rate at which hyponatremia develops. Premonitory or early symptoms include nausea, vomiting, anorexia, disorientation, headache, fatigue, weakness, irritability, lethargy, confusion, and muscle cramps. Acute severe hyponatremia causes cerebral edema that can lead to coma, irreversible neurologic damage, and supratentorial cerebral herniation resulting in respiratory arrest from brain stem compression and death. In contrast, patients with chronic hyponatremia are often asymptomatic, even with serum sodium level as low as 120 mEq/L (Adroqué, 2005). As hyponatremia progresses, above-mentioned premonitory, nonspecific symptoms are followed by neuropsychiatric symptoms such as seizures, hemiplegia, dysarthria, hallucinations, tremor, and coma. Patients may demonstrate an impaired response to verbal and painful stimuli, and exhibit bizarre behavior or experience auditory or visual hallucinations (Fraser & Arieff, 1997). These psychiatric symptoms may mimic the manifestations of primary psychiatric disorders such as schizophrenia, and thus clinicians should be careful not to be misled into a judgment that the primary disorder is exacerbated. It also should be considered that compulsive water consumption in the late afternoon and evening may impair mental status and further exacerbate psychiatric symptoms (Siegel, 2008).

Although hyponatremia is derived from a variety of etiologies and classified into several types according to plasma and urine osmolarity as well as the volume of the total body water (Reddy & Mooradian, 2009), hyponatremic encephalopathy in psychiatric patients is usually the so-called polydipsia-hyponatremia syndrome (psychogenic polydipsia) with hypotonic plasma osmolarity and euvolemic status of the total body water. However, compulsive water drinking alone is usually not sufficient to induce marked hyponatremia, because the normal kidney should theoretically be able to excrete water in excess of 20 liters per day and most patients actually ingest less water than that theoretically required (Vieweg

et al., 1987; Fraser & Arieff, 1997). As demonstrated by Goldman et al. (1988), the patients with polydipsia and hyponatremia are accompanied with impaired maximal urinary dilution and free-water clearance in response to water loading, suggesting renal abnormally enhanced sensitivity to low concentrations of arginine vasopressin (AVP). They also showed that the patients with a history of polydipsia and hyponatremia demonstrated a higher serum AVP levels as well as greater thirst independent of their serum osmolarity after receiving an infusion of hypertonic saline, suggestive of a downward shift in the threshold for AVP release and defect of osmoregulation of thirst, respectively (Siegel, 2008).

Most psychiatric patients with polydipsia-hyponatremia syndrome are thus associated with maladapted water and electrolyte homeostasis sustained principally by the action of neurohypophyseal antidiuretic hormone AVP. It has been demonstrated that lots of psychotropic drugs including antipsychotics, antidepressants, and anticonvulsants, can cause syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Spigset & Hedenmalm, 1995; Bhuvaneswar et al., 2009; Reddy & Mooradian, 2009), and that antipsychotic-induced hyponatremia is most likely a result of SIADH (Meulendijks, 2010). Vieweg et al. (1987) also postulated that the syndrome of self-induced water intoxication and psychosis (SIWIP) was a subcategory of SIADH, with hypoosmolality and hyponatremia induced synergistically by polydipsia and released AVP, both of which were stimulated by psychosis. In the schizophrenic patients with polydipsia-hyponatremia syndrome, plasma AVP levels were shown to rise sharply after the pharmacological induction of psychotic symptoms with methylphenidate (Goldman et al., 1997). This mechanism may underlie the episodic escalation of polydipsia observed in psychotically exacerbated patients [psychosis, intermittent hyponatremia, and polydipsia (PIP) syndrome (Leadbetter et al., 1994)], which sometimes result in severe, life-threatening hyponatremic encephalopathy (Vieweg et al., 1985).

Treatment of hyponatremic symptoms in psychiatric patients depends on their severity as well as the rate of development (Siegel, 2008). Acute severe hyponatremic encephalopathy could be life-threatening, which thus has to be treated as an emergency with hypertonic saline to prevent cerebral edema. On the other hand, chronic hyponatremia associated with psychogenic polydipsia is optimally managed with behavioral treatments including fluid restriction (Dundas et al., 2007) and removal of, if identified, underlying causes. Careful monitoring of diurnal body weight change for the PIP syndrome patients is useful to recognize hyponatremic episodes at an earlier stage and prevent sequelae due to severe hyponatremic encephalopathy (Leadbetter et al., 1994). In any case, osmotic demyelination, such as central pontine myelinolysis, possibly associated with overaggressive correction of serum sodium concentrations (more than 10 mmol/L in 24 hours, 18 mmol/L in 48 hours, and 20 mmol/L in 72 hours), should be avoided (Sterns et al., 2009). Specific pharmacological treatment with democlocycline or AVP receptor antagonists (aquaretics) for chronic hyponatremia in psychiatric patients may become standardized in the near future (Siegel, 2008).

5.2 Valproate-induced hyperammonemic encephalopathy

It has been known that valproic acid occasionally induces hyperammonemic encephalopathy in patients with otherwise normal hepatic function (Carr & Shrewsbury, 2007; Marie-José, 2007). In most cases, encephalopathic symptoms appear in a few days after

initiation of valproate therapy, with exceptional case reports with onset after longer therapeutic periods for several months or years. There remains controversy as to whether symptoms have any relationship to daily dose or plasma concentration of valproic acid. In a prospective study, the significantly higher prevalence of asymptomatic hyperammonemia was found in the psychiatric patients treated with valproate than in the control, and there was a positive correlation between serum valproic acid concentrations and ammonia levels (Raja & Azzoni, 2002). Nevertheless, it should be noted that many cases with symptomatic encephalopathic symptoms reported up to date have serum valproic acid concentrations within therapeutic range (Carr & Shrewsbury, 2007; Marie-José, 2007).

5.3 Transient splenial lesion of the corpus callosum

Since several antiepileptic drugs have been widely prescribed as effective mood stabilizers in psychiatric practice (Grunze, 2010), all psychiatrists should be familiar with adverse phenomena associated with them. With widespread use of magnetic resonance imaging (MRI), a characteristic discrete focal lesion limited to the central area of the splenium of the corpus callosum has been recognized to occur in epileptic patients receiving antiepileptic drugs (S.S. Kim et al., 1999; Polster et al., 2001). Although the pathophysiological mechanisms of this lesion are still obscure, antiepileptics appear to be implicated as pathogenetic or triggering factors at least in some cases. Indeed, the same lesion has been reported also in the non-epileptic patients treated with antiepileptic drugs (Maeda et al., 2003; Honda et al., 2006). Some patients developed the lesion on treatment with antiepileptic drugs (Kim et al., 1999; Polster et al., 2001; Maeda et al., 2003), while others subsequent to withdrawal of them (Polster et al., 2001; Gürtler et al., 2005; Honda et al., 2006).

The lesion is usually detected accidentally by MRI, accompanied with no apparent clinical signs and symptoms. It is characterized with an isolated oval-shaped abnormal signal in MRI located in the central area of the splenium, no enhancement on post-contrast MRI, and complete reversibility without specific treatment. In consideration of its benign outcome, unnecessary invasive examination and therapeutic intervention should be avoided (Maeda et al., 2003).

5.4 Miscellaneous

Acute onset alterations in CNS function are derived from a variety of etiological factors. When specific pathogenetic processes directly invading the brain (e.g., vascular, infectious, and neoplastic diseases) are ruled out, other diffuse, multifocal, or metabolic causes should be considered (Posner et al., 2007). If treated with psychotropic drugs, the possibility of direct or indirect contribution of these chemicals to the pathophysiological status should be always evaluated with caution. The SIADH associated with psychotropic drugs and valproate-induced hyperammonemia, both of which have been described above, exemplify such implication. In addition, many psychotropic drugs, especially antidepressants and antipsychotics, have been shown to possess ability to reduce seizure threshold and to provoke epileptic seizures (Alldredge, 1999; Pisani et al., 2002). Antipsychotics, in particular atypical antipsychotics such as clozapine and olanzapine, are reported to be associated with an increased risk of obesity, diabetes, and metabolic syndrome (Scheen & De Hert, 2007; Smith et al., 2008) and in the worse case it can result in fatal hyperglycemic encephalopathy (Koller & Doraiswamy, 2002; Wehring et al., 2003). Lithium, a widely used mood stabilizer,

increases the risk of hypothyroidism, which can range from subclinical to life-threatening myxedema coma (Bhuvaneswar et al., 2009; Thomas et al., 2010). A case of Hashimoto's encephalopathy possibly induced by lithium was also reported (Nagamine et al., 2008).

6. Concluding remarks

In these two decades, pharmacotherapy with psychotropic drugs for mentally ill patients has been dramatically changed. Classical prototypal antipsychotics, such as chlorpromazine and haloperidol, have been replaced with atypical antipsychotic drugs for the treatment of psychotic patients. As for the pharmacotherapy for mood disorders, total antidepressant prescribing has increased, especially in 1990s with exponential increase in prescriptions of SSRIs (Donoghue, 1998; Middleton, et al., 2001). This remarkable rise in SSRIs prescribing experienced in the United Kingdom may be attributable, in part, to the Defeat Depression Campaign (Paykel et al., 1997), which was undertaken from 1992 to 1996. However, the similar trends in antidepressant prescriptions have also been observed in all other developed countries worldwide. The vigorous marketing promoted by pharmaceutical companies probably contributed to the overwhelming spread of SSRIs in 1990s to a great extent (McHenry, 2005). In addition, SSRIs have been more and more prescribed not only for depression but also for a number of other psychiatric diagnoses such as anxiety, eating, impulse-control, and personality disorders. Many antiepileptic drugs are also prescribed generally for psychiatric patients in anticipation of their mood stabilizing effects.

In general, the newly developed psychotropic drugs are believed to be safer and more tolerable than older drugs. The apparent lowered risk of adverse effects of novel drugs may facilitate the clinician's attitude for prescribing these psychotropic drugs automatically, and sometimes indiscreetly. However, there is no efficacious drug without adverse side effects. All clinicians who have an occasion to prescribe psychotropic drugs, or to see the patients treated with them, should be familiar with adverse symptoms associated with them.

This chapter focuses on the adverse effects of psychotropic drugs involving altered CNS function. Although nonspecific CNS reaction due to overdosed psychotropic drugs has not been included, it should be always taken into consideration when the patients treated with psychotropic drugs exhibit inexplicable CNS symptoms. Lithium-induced toxic encephalopathy has been reported to occur even when serum lithium levels are kept within a therapeutic range (Sheean, 1991). When adverse effects on CNS function are presented apparently as psychiatric symptoms, these should not be misdiagnosed as exacerbation of the primary psychiatric disorder. Such misjudgment may lead to the clinical decision to increase the offending drugs or to add other kinds of psychotropic drugs, which could further complicate matters and delay appropriate intervention. Even in the case of the idiosyncratic adverse effects such as NMS, the most efficacious way to abort the syndrome without serious sequelae should be early recognition of, and prompt appropriate intervention in, the clinical symptoms at the incipient stage.

Pharmacotherapy becomes meaningfully efficacious only when it is considered in the whole therapeutic framework and associated synergistically with other psychosocial therapies. In general, most psychotropic drugs have only limited therapeutic effects, which never cure the psychiatric diseases themselves but relieve the symptoms partially. The efficacy of SSRIs in depressed patients over placebo has been shown to be minimal, if any, by recent meta-

analyses (Moncrieff & Kirsch, 2005). While it is true that pharmacotherapy bring enormous benefit to some patients, I have also been aware of many cases at a disadvantage associated with thoughtless or unnecessary use of psychotropic drugs. The prudent and conscientious decision-making for pharmacotherapy in consideration of the quality of life of the individual patient is highly warranted.

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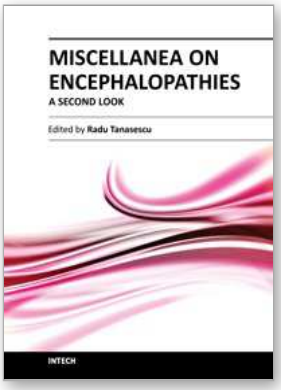

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