

Atypical Neuroleptic Malignant Syndrome or Serotonin Toxicity Associated with Atypical Antipsychotics?

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Abstract: Atypical antipsychotics and selective serotonin reuptake inhibitors (SSRIs) have been prescribed extensively, often in combination with each other. When toxic encephalopathy develops with neuromuscular and autonomic symptoms in a patient taking medication including atypical antipsychotics, it has tended to be diagnosed as neuroleptic malignant syndrome (NMS). However, there have recently been several case reports where the diagnosis of serotonin syndrome is given or raised as a likely differential diagnosis to such cases. In the present review, the author addressed himself to the issues surrounding the neurotoxic reaction to the treatment regimen containing atypical antipsychotics, focusing on the "atypical" forms of NMS and pathophysiological as well as clinical features of serotonin toxicity. Although NMS is idiosyncratic in nature, it appears practically useful to comprehend this syndrome as a spectrum-based concept. Likewise, serotonin toxicity is a broad spectrum of clinical syndromes in close connection with serotomimetic drug use, including varied severity. Some of atypical antipsychotics, i.e., perospirone, aripiprazole, ziprasidone, clozapine, and quetiapine, have been shown to behave as partial agonists at 5-HT_{1A} receptors, providing direct evidence that these atypical antipsychotics are serotomimetic *per se*. The reciprocal interaction between the dopaminergic and serotonergic systems disturbed by either dopaminergic blockers or serotonergic enhancers leads to the disruption of homeostasis, with typical forms of NMS and serotonin syndrome representing the ends of the common pathophysiological background. The practical and flexible way to consider and manage such cases with updated knowledge derived from basic research should be warranted to be beneficial to our patients.

Keywords: Neuroleptic malignant syndrome, serotonin toxicity, serotonin syndrome, atypical antipsychotics, 5-HTT_{1A} receptor, partial agonist.

INTRODUCTION

Half a century has passed since the prototypes of psychotropic drugs were introduced into the psychiatric clinical practice. These older psychotropic drugs have been replaced with a new generation of drugs, which comprise selective serotonin reuptake inhibitors (SSRIs), reversible and selective monoamine oxidase inhibitors (MAOIs), atypical antipsychotics, antiepileptics as mood stabilizers, and antidementia agents. Especially, newer atypical antipsychotics and SSRIs have been prescribed greatly across diagnoses in the past decade [1,2]. Although it is generally accepted that the newer drugs are safer and better tolerated than older drugs, adverse effects associated with psychotropic drugs are still problematic issue to be challenged.

Most experts are in favor of psychopharmacological monotherapy, as also stressed in many psychiatric textbooks. In practice, however, this is not the case. The survey of psychotropic drug use in Austria has shown that only 8 to 22 % of the patients undergo psychopharmacological monotherapy [3]. Furthermore, there is a trend towards more frequent use of drug combinations over time in recent years [1,2]. Thus, risks of adverse effects due to multiple pharmacokinetic or pharmacodynamic interactions which have to be considered are increasing.

Among diverse adverse reactions to pharmacotherapy with psychotropic drugs, neuroleptic malignant syndrome (NMS) induced by antipsychotics has been one of the most serious complications, that is potentially life-threatening. NMS occurs as an idiosyncratic drug reaction, characterized by muscle rigidity, hyperthermia, autonomic instability, altered mental status, and evidence of muscle injury (e.g., elevated creatine phosphokinase (CPK) levels) [4-10]. Although the exact pathogenesis underlying NMS has not been fully understood, it is generally accepted that a massive and sudden reduction in dopaminergic activity secondary to neuroleptic-induced dopamine D₂ receptor blockade plays an important and primary role in initiating the serious sequential processes of this syndrome [11,12]. NMS is thought to occur as an idiosyncratic drug reaction that is not dose-related. On the other hand, it has also been suggested that use of high-potency conventional antipsychotics is associated with a greater risk of NMS compared with low-potency antipsychotics [13], and that the higher doses of antipsychotics are one of the risk factors for the development of NMS [14]. As atypical antipsychotics have generally lower potency as a dopamine receptor antagonist than typical antipsychotics, it was anticipated that they would be less likely to cause NMS. However, substantial cases of NMS associated with atypical antipsychotics have been reported so far, and it is evident that the atypical antipsychotics are not entirely free of the risk of NMS [9,15].

Another severe medical complication associated with psychotropic pharmacotherapy is serotonin toxicity (or serotonin syndrome) [16-26]. In contrast with the idiopathic nature of NMS, serotonin toxicity is a predictable consequence

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of excess serotonergic transmission, which occurs following the use of serotomimetic agents such as serotonin reuptake inhibitors, serotonin precursors, and monoamine oxidase inhibitors (MAOIs), most often by the concurrent use of two or more drugs with different mechanisms of action. This toxicity is characterized by a triad of symptoms including cognitive-behavioral changes, neuromuscular abnormalities, and autonomic instability, almost all of which are similar to or identical with those of NMS. Because of this overlapping of symptoms, it is often very difficult or even impossible to discriminate serotonin toxicity from NMS clinically, especially when both antipsychotics and serotonergic agents have been recently added to a treatment regimen or escalating doses of either have been used [25]. Differential diagnosis between serotonin toxicity and NMS is becoming a matter of increasing interest, because atypical antipsychotics and SSRIs are prescribed quite frequently, and often in combination together or with other psychotropic drugs.

The aim of this brief review is not to describe NMS or serotonin toxicity in a comprehensive manner, but to contribute to clinical psychiatry as well as psychopharmacology by presenting the flexible and practical way how to consider and treat the adverse reaction, which should be differentiated from NMS or serotonin toxicity, to regimen including atypical antipsychotics. The underlying mechanisms of action of atypical antipsychotics for the reason why serotonin toxicity should be taken into consideration as a differential diagnosis were also presented.

NMS ASSOCIATED WITH ATYPICAL ANTIPSYCHOTICS

Clozapine is a prototypal drug of atypical antipsychotics with low incidence of extrapyramidal symptoms. Since poorly controlled extrapyramidal symptoms associated with antipsychotic pharmacotherapy were thought to be a risk factor for the development of NMS [27] or “neuroleptic-induced extrapyramidal symptoms with fever” [28], the introduction of clozapine had raised the hope that it would not produce NMS. Upon six cases which had been sporadically reported as NMS apparently related to clozapine therapy, Weller and Kornhuber [29] presented a comment that did not favor the notion that clozapine caused NMS. Thornberg and Ereshefsky [30] were also somewhat discreet in recognizing a causal relationship between clozapine monotherapy and NMS. However, the subsequent many case reports and several review articles [15, 31-36] clearly indicate that clozapine is capable of inducing NMS, even in a typical and full-blown form. The exact incidence of NMS induced by clozapine is difficult to estimate, since almost all studies are retrospective, other medications such as lithium and other antipsychotics are often used concomitantly with clozapine [32,34], and the diagnosis of NMS is largely varied depending on the degree of stringency of the criteria used [15,33,34,37]. Although there has been a report indicating that clozapine is significantly less likely to cause NMS than are typical antipsychotics such as haloperidol and fluphenazine [38], another shows that the incidence of NMS with clozapine is comparable with that for the conventional antipsychotics [31].

The atypical antipsychotics subsequent to clozapine, i.e., risperidone, olanzapine, and quetiapine have been reported to

be associated with NMS likewise [15,33,35,36]. As for ziprasidone, at least six cases of probable NMS in association with its use have also been reported so far [39-44]. There have been two case reports of NMS in connection with perospirone [45,46], another serotonin-dopamine antagonist which was developed by a Japanese pharmaceutical company and has been available as an atypical antipsychotic drug solely in Japan [47].

Aripiprazole is referred to as a third generation antipsychotic, since the proposed mechanisms of action for its therapeutic effectiveness for the symptoms of schizophrenia are fundamentally different from any other previous antipsychotics in that it is a partial agonist at dopamine D₂ receptors whereas all other first and second generation antipsychotics are antagonists [48]. In such a sense, this atypical antipsychotic drug has also been described as a “dopamine system stabilizer” [49,50]. Based on its unique psychopharmacological profile, it is theoretically supposed that excessive hypodopaminergic state thought to be responsible for the development of NMS is unlikely to stem from treatment with aripiprazole. However, there have been several case reports of NMS possibly in association with aripiprazole so far [51-59]. Although aripiprazole certainly behaves as a partial agonist at dopamine D₂ receptors in many experimental systems, its intrinsic activity as an agonist at dopamine D₂ receptors is, at least in rat striatal membranes, minimal as compared with other dopaminergic agonists such as *R*(-)-apomorphine and bromocriptine [60,61]. As discussed in a previous review article [61], the intrinsic activities of partial agonists at dopamine D₂ receptors should be as low as that of aripiprazole in order to be effective antipsychotics against positive symptoms, though the optimal intrinsic activity for a patient may be varied depending on the individuality and targeted symptoms. Considering such a low intrinsic activity of aripiprazole, it may be unstudied to meet with sporadic cases of NMS related with its use.

To conclude the above, it can be clearly indicated that all atypical antipsychotics commercially available up to date, including the third generation antipsychotic aripiprazole, are not entirely free of the risk of NMS, as long as they have a pharmacological feature as antagonists at dopamine D₂ receptors.

ATYPICAL NMS

Immediately after the three cases of presumed aripiprazole-induced NMS were reported [52,53,57], Strawn [62] raised a comment to point out the “atypical” features reported in these cases, e.g., lack of extreme hyperthermia, grossly elevated CPK, and ‘lead-pipe’ muscle rigidity, with concern for the validity of the diagnosis as NMS in these patients treated with aripiprazole. Although it has been proved that typical or considerably severe form of NMS can certainly develop in association with aripiprazole in other case reports [54,58], the comment upon “atypical” features of NMS [62] may also be applicable to many NMS cases reported to be related with other atypical antipsychotics than aripiprazole [63].

Although NMS is idiosyncratic in nature, the extent of the severity for the symptoms presented is considerably variable from case to case. Even with conventional antipsychotics such as haloperidol and chlorpromazine, incomplete

forms of NMS without severe hyperthermia and/or muscle rigidity, or milder symptoms of NMS that abated without cessation of neuroleptic treatment have been described [64-70]. These atypical or milder cases of NMS have been nowadays usually termed "atypical NMS" [63,66,71-73], though previously they were also designated "forms frustes" [5,74], "milder variant" [67], or "incipient" [70].

Many cases of atypical NMS are unable to be diagnosed as NMS, at least as a definite case, if we adhere to the stringent diagnostic criteria. For instance, the Diagnostic and Statistical Manual of Mental Disorders, Forth Edition, Text Revision (DSM-IV-TR) [75] raises severe muscle rigidity and elevated temperature associated with the use of a neuroleptic medication as necessary cardinal features for the diagnosis of NMS, along with two or more of the following symptoms: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leucocytosis, or laboratory evidence of muscle injury (e.g., elevated CPK). Several other diagnostic criteria also identify hyperthermia and muscle rigidity as major symptoms, both of which should be present concurrently to be met for a diagnosis of definite NMS [7,67,76]. However, the definition of hyperthermia has been varied according to the criterion, i.e., $\geq 38.0^{\circ}\text{C}$ [7], $\geq 37.5^{\circ}\text{C}$ [76], and $\geq 37.2^{\circ}\text{C}$ [67]. Moreover, another set of criteria [4] allows the diagnosis of NMS in patients either with all three major symptoms (fever, rigidity, and elevated CPK level) or with two major and four minor manifestations (tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, leukocytosis).

With the predominant use of atypical antipsychotics in recent years, more attention has been directed to the existence of these atypical cases of NMS [15,63]. However, it is still controversial whether the "atypical NMS" is more likely with atypical antipsychotics than with conventional antipsychotics. Since the presentation of NMS even with typical antipsychotics can be heterogeneous and variable, some investigators are cautious in hastily ascribing milder and atypical cases associated with novel antipsychotics to NMS [29,33,43,77]. Ananth *et al.* [36] concluded that atypical antipsychotic drug-induced NMS manifestations were of similar nature and severity as those produced by conventional antipsychotics. For example, the incidence of extrapyramidal symptoms associated with NMS induced by atypical antipsychotics (78%) was described to be comparable to that for the cases of NMS induced by conventional antipsychotics (95%). Nevertheless, many researchers are under the impression that the manifestations of NMS precipitated by atypical antipsychotics are often associated with only partial or incomplete characteristics. To support this notion, though partially, is the study on the cases of NMS induced by atypical antipsychotics reported by Caroff *et al.* [15], in which second-generation antipsychotics (clozapine, risperidone and olanzapine) have been found to be significantly less likely than first-generation antipsychotics to be associated with body temperatures exceeding 38°C or 40°C . In this investigation, it has also been reported that clozapine is associated with a lower rate of rigidity (79%), although not statistically significant, than olanzapine (89%), risperidone (95%) and typical antipsychotics (91%). Likewise, clozapine-associated NMS has been reported to be somewhat different from those associated with traditional antipsychot-

ics, with less prominent fever and extrapyramidal symptoms and a lower rise in CPK levels [31,34].

Although it is difficult to determine whether an atypical presentation represents a prodromal or abortive stage that should progress toward a fulminant state without any intervention, the awareness of atypical NMS cases associated either typical or atypical antipsychotics has promoted an important concept that NMS may be a spectrum disorder [37,63,68,78-81]. This concept may confuse our understanding of NMS with a risk of its overzealous use to lead to mismanagement [79]. However, it appears practically useful to comprehend NMS as a spectrum-based concept [63,81] (Fig. 1), to facilitate prompt diagnosis and treatment [70,82], though it may be difficult to determine from which stage of this continuum it should be termed NMS.

SOME ATYPICAL ANTIPSYCHOTICS ARE 5-HT_{1A} RECEPTOR AGONISTS

From the pathophysiological as well as phenomenological points of view, the existence of "atypical" forms of NMS associated with atypical antipsychotics reminds us of another important concept that NMS may be part of a larger spectrum with likely common or overlapping underlying mechanisms and apparently common symptoms. Choi-Kain and Pope [73] have designated this spectrum "malignant cerebrotoxic syndrome", which includes serotonin syndrome, malignant hyperthermia and lethal catatonia in addition to NMS. The similar concept was also raised by Fink and Taylor [83], who lumped catatonia, malignant catatonia, NMS, toxic serotonin syndrome, delirious mania and periodic catatonia under the general rubric of "syndromes of catatonia". It is beyond my scope to validate or criticize these notions, though the so-called "lethal catatonia" and its associates that had been described before the era of psychotropic pharmacotherapy should be, in my opinion, clearly differentiated from NMS, as pointed out by Castillo *et al.* [84]. It also appears feasible to recognize NMS as a clinical entity different from malignant hyperthermia, a hypermetabolic state of skeletal muscle suddenly precipitated by exposure to potent volatile anesthetics such as halothane, sevoflurane, desflurane and the depolarizing muscle relaxant succinylcholine [7], although there may be phenomenological similarities and pathophysiological overlapping between both disorders [85]. Apart from the above-mentioned concept of spectrum disorders including NMS, I would like to draw the readers' attention hereon to the necessity of considering serotonin toxicity (or serotonin syndrome) as a differential diagnosis when we see the NMS-like symptoms developed in a patient treated with psychotropic regimen including atypical antipsychotics.

As with NMS, the diagnosis of serotonin syndrome is based on exclusion, with differential diagnosis of prime importance. In the suggested diagnostic criteria for serotonin syndrome [16,24], there is the item, to exclude NMS, that a neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms. This description appears sound in general and necessary to rule out NMS, almost all symptoms of which are identical to or indistinguishable from those of serotonin syndrome. However, it may be necessary to update or supplement this item to provide clinicians with newer information that some antipsychot-

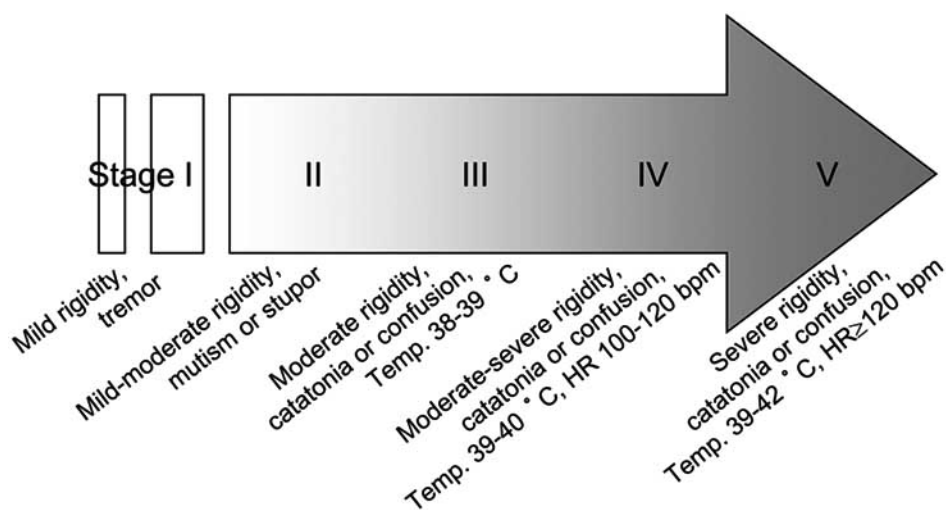


Fig. (1). The spectrum concept of NMS. Although NMS is regarded as idiosyncratic by nature, the extent of severity for the symptoms presented is considerably variable from case to case and depending on its developing stages. The existence of “atypical” or “milder” cases of NMS has developed the spectrum-based concept of NMS [63,81]. Stages I to V are derived from the report by Woodbury and Woodbury [81].

chotics, atypical ones in particular, are not only antagonistic at dopamine receptors but also serotomimetic *per se*.

The prototypal atypical antipsychotic clozapine was shown to be a partial agonist at human 5-HT_{1A} receptors expressed in Chinese Hamster Ovary cells [86]. Subsequently, it was reported with the same experimental system that several antipsychotics including ziprasidone, quetiapine, and aripiprazole also exhibited partial agonist activity at 5-HT_{1A} receptors [87,88]. These agonistic effects of several antipsychotics at 5-HT_{1A} receptors have been verified also in naturally occurring receptors in human [89] as well as rat [90,91] brain tissue. The characteristics of several antipsychotics and some referential serotonergic agents as an agonist at rat hip-

pocampal 5-HT_{1A} receptors are summarized in Table 1 [91-93]. Given their potencies and relative efficacies as compared with those of buspirone and tandospirone, well-known partial 5-HT_{1A} receptor agonists clinically available as anxiolytics [94,95], the properties of these antipsychotics as partial agonists at 5-HT_{1A} receptors appear worthy of being considered.

The potential roles of 5-HT_{1A} receptors implicated in the pathophysiology and pharmacotherapy of schizophrenia have been discussed chiefly in the context of their therapeutic advantage [96,97]. Similar to almost all efficacious drugs, however, 5-HT_{1A} receptor agonists are double-edged swords. Serotonin toxicity possibly associated with the use of buspi-

Table 1. Agonist Properties at 5-HT_{1A} Receptors of Antipsychotics and Referential Serotonergic Drugs in Rat Hippocampal Membranes Determined by Guanosine-5'-O-(3-[³⁵S]thio)-Triphosphate ([³⁵S]GTPγS) Binding Assay (Modified from [91-93])

| Compound (Therapeutic Daily Dose) | EC ₅₀ (μM) | E _{max} (% 5-HT) |
|-----------------------------------|-----------------------|---------------------------|
| 5-HT | 0.074 | 100 |
| Tandospirone (30-60 mg) | 0.53 | 36 |
| Buspirone (15-60 mg) | 4.6 | 8 |
| Ipsapirone | —* | —* |
| Perospirone (12-48 mg) | 0.027 | 14 |
| Aripiprazole (6-30 mg) | 0.045 | 32 |
| Ziprasidone (20-80 mg) | 0.48 | 28 |
| Nemonapride (9-60 mg) | 0.79 | 45 |
| Clozapine (100-900 mg) | 3.9 | 44 |
| Quetiapine (50-750 mg) | 26 | 36 |
| Olanzapine (10-20 mg) | —* | —* |
| Risperidone (0.5-8 mg) | —* | —* |
| Zotepine (75-450 mg) | —* | — |

*Inactive as an agonist.

rone in combination with other concurrently prescribed serotonergic agents (SSRIs in most cases) has been reported [98-108]. There are also at least two case reports published demonstrating serotonin toxicity developed in association with tandospirone, alone [109] or in combination with trazodone [110].

Of course, it is unlikely that all clinical symptoms of serotonin syndrome stem from the excess stimulation of 5-HT_{1A} receptors alone, although many researchers stress the important role of this receptor subtype in the pathogenesis of serotonin syndrome [16-18,22,23,25]. We should be cautiously aware of the fact that the term "serotonin syndrome" in humans was originated from the serotonin behavioral syndrome defined in rodents [111], and that there is no evidence to recognize these two syndromes as identical or even similar ones in terms of phenomenology or underlying mechanisms [112]. The animal behavioral model, produced by compounds that either increase synaptic serotonin content or stimulate serotonin receptors, e.g., administration of the serotonin precursors such as 5-hydroxytryptophan (5-HTP) and L-tryptophan plus MAOI, is characterized by resting tremor, rigidity or hypertonicity, reciprocal forepaw treading, hindlimb abduction, Straub tail, and lateral head weaving [113]. Although several lines of evidence have clearly shown that most of these features of the serotonin behavioral syndrome are mediated by postsynaptic 5-HT_{1A} receptors, head twitches in mice and an equivalent behavior in rats, referred to as "wet dog shakes", are both shown to be mediated by 5-HT_{2A} receptors. Furthermore, 5-HT_{1A} receptors and 5-HT_{2A} receptors are known to mediate hypothermia and hyperthermia, respectively, and the latter of which occurs often as one of the major features in typical clinical cases of serotonin syndrome [16,17,19,23]. Although hyperthermia was not included as a part of the original definition of serotonin behavioral syndrome in animal experiments [113], 5-HT_{2A} antagonists were shown to prevent hyperthermia and lethality dramatically in an animal model of the serotonin syndrome produced by 5-HTP and the MAOI clorgyline [114,115]. Also in clinical serotonin toxicity, especially in severer cases with hyperthermia and extreme hypertonicity, the pathophysiological involvement of 5-HT_{2A} receptors rather than 5-HT_{1A} receptors appears of prime importance [112,116].

In spite of the potential involvement of other 5-HT receptor subtypes than 5-HT_{1A} receptors, especially 5-HT_{2A} receptors as mentioned above, in pathogenesis and pharmacotherapy in serotonin syndrome, it appears of considerable help for the clinicians to keep in mind the experimental results indicating several antipsychotics including most atypical drugs behave as partial 5-HT_{1A} receptor agonists and the necessity of considering serotonin syndrome as a differential diagnosis in patients suffering from NMS-like symptoms subsequent to the prescription containing antipsychotics.

SEROTONIN TOXICITY OR NMS?

As mentioned above, the term serotonin syndrome may be problematic; since it is sometimes used in nonspecific sense applied commonly either for the clinical toxic syndrome occurring in humans or for the behavioral syndrome observed in rodents, possibly leading to confusion or misconception. Additionally, this term tends to promote the in-

correct presumption that it is an idiosyncratic response like NMS [20] (but see also [19]). According to these reasons, some investigators prefer the terms "serotonin toxicity" or "toxic serotomimetic reaction" as alternative descriptions to refer to the clinical state that seems reasonably attributable to excessive serotonin or hyperstimulated 5-HT receptors [20,112,117]. In this review, "serotonin toxicity" is preferred as a general term to refer to the broad spectrum of clinical syndromes in close connection with serotomimetic drug use [24,26] (Fig. 2), including varied severity from mild signs of excess 5-HT, such as tremor and/or diarrhea, to the typical "serotonin syndrome" with fulminant features characterized by a triad of clinical symptoms consisting of autonomic signs, neuromuscular changes, and altered mental status, being potentially life-threatening in the severest cases designated "serotonin storm" or "serotonin crisis" [112].

Hegerl *et al.* [118] developed the "serotonin syndrome scale" to assess the severity of serotonin toxicity and reported that the scores in depressed patients treated with paroxetine significantly correlated positively with paroxetine plasma levels and negatively with the loudness dependence of the auditory evoked potentials, a neurophysiological measure that was supposed to be lower in higher central serotonergic neurotransmission. These experimental results are consistent with the clinical fact that the typical and classical cases with serotonin syndrome, at least those in severe forms, have been reported in the patients treated with a simultaneous combination of two drugs that increase 5-HT availability by separate methods, especially when involving MAOIs [17]. It has been shown that the combination of two serotonergic drugs including MAOIs induces marked elevation of 5-HT levels in rats determined in microdialysis studies, and that the degree of elevated 5-HT levels roughly parallels the severity of serotonin toxicity in humans as well as serotonin syndrome in rats [117].

With the increasing awareness of high risk of developing serious serotonin syndrome subsequent to drug combinations between MAOIs and other serotonergic antidepressants such as SSRIs, clomipramine and venlafaxine, we may now hardly see the patients with severe clinical features of serotonin syndrome precipitated with such risky drug combinations in usual practical setting. Instead, we are concerned with the potential increment of moderate or milder serotonin toxicity cases associated with SSRIs and/or atypical antipsychotics, both of which have been prescribed recently more and more frequently [1,2], often in combination with each other or with other psychotropic drugs. Given these clinical situations along with the afore-mentioned "atypical" NMS precipitated by atypical antipsychotics, it appears a matter of considerable interest to pay regard to both NMS and serotonin toxicity as differential diagnoses in patients who develop toxic reaction to the prescription containing atypical antipsychotics.

To differentiate NMS from serotonin syndrome may not be so difficult when the patient is suffering from the typical clinical features of either syndrome [19,20,112]. As described in many reviews, such clinical features as myoclonus, hyperreflexia, shivering, mydriasis, and gastrointestinal symptoms are more frequently observed in serotonin syndrome, whereas severe "lead-pipe" rigidity and bradykinesia are characteristics of NMS. Additionally, slower onset

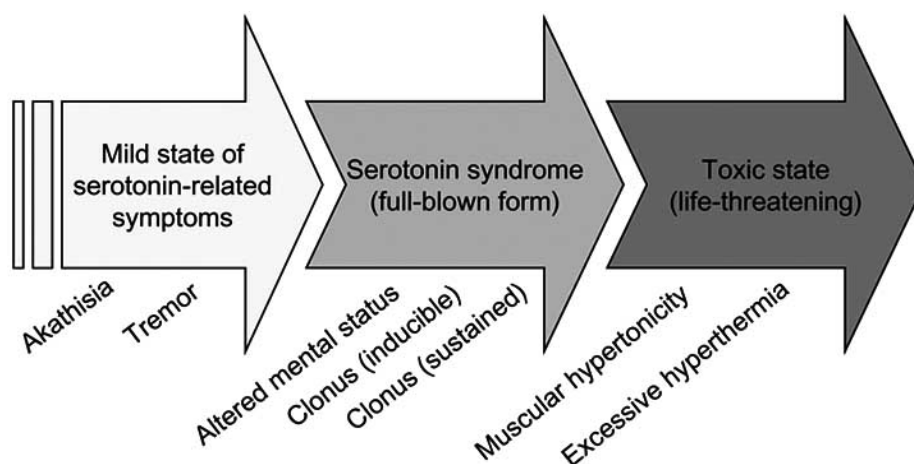


Fig. (2). The spectrum concept of serotonin toxicity. On the basis of the severity of overall clinical presentation, serotonin toxicity is further classified into three groups as: (1) mild state of serotonin-related symptoms; (2) serotonin syndrome (full-blown form); (3) toxic state (often life-threatening, and also designated “serotonin storm” or “serotonin crisis” [112]) [24]. Although depicted separately in this figure, it should be supposed as a continuum without definite gaps between the groups.

of days to weeks as well as slower progression over 24-72 h in NMS are in contrast with both rapid onset and rapid progression in minutes to hours in serotonin syndrome in association with offending drugs. Nevertheless, there could be still many cases where difficulty arises with the differential diagnosis between NMS and serotonin toxicity (e.g. [119]).

In such cases, too much adherence to the rigid dichotomy may be inappropriate, although we should do our continuous best to make a differential diagnosis between NMS and serotonin toxicity. Supposedly, the reciprocal balance between the dopaminergic and serotonergic systems may become disrupted by either dopaminergic blockers or serotonergic enhancers, with these two syndromes representing different aspects of the common pathophysiological background (Fig. 3). From the clinical and practical points of view, of the most importance is to recognize any signs and/or symptoms possibly indicative of toxic reactions to the prescribed psychotropic drugs that potentially develop into identifiable NMS (Fig. 1) or serotonin syndrome (Fig. 2) if without any intervention, e.g., unexpected changes in mental status, new-onset catatonia, episodic tachycardia, tachypnea or hypertension, dysarthria, dysphagia, diaphoresis, sialorrhea, incontinence, low-grade temperature elevations, rigidity, myoclonus, tremor or other extrapyramidal signs unresponsive or resistant to antiparkinsonian drugs, and unexplained elevations in serum CPK. The prompt removal of the possible offending psychotropic drugs, along with supportive care comprising the administration of intravenous fluids and correction of vital signs on demand, may be sufficient at this stage. Mild to moderate serotonin toxicity is known to be usually self-limited and resolve quickly within 24 hours after discontinuation of precipitating drugs. Therefore, if clinical features tend to be prolonged and aggravated even with appropriate treatment, the diagnosis of NMS, an idiosyncratic reaction to antipsychotics, might be more likely, unless the regimen includes MAOIs or MDMA (3,4-methyl-enedioxymethamphetamine; Ecstasy), drugs with the potential of inducing higher elevation of 5-HT levels implicated in the severest forms of serotonin toxicity referred to as “serotonin storm” or “serotonin crisis” [117]. Alternatively, the

Alternatively, the possibility of vicious cycle involving complications such as rhabdomyolysis, acute renal failure, metabolic acidosis, electrolytes imbalance, aspiration pneumonia, pulmonary embolism, disseminated intravascular coagulation (DIC), seizures, and so on, should be taken into consideration. In severer cases, especially when accompanied with extreme hyperthermia, more intensive care with mechanical ventilation, aggressive external cooling, muscle relaxation by benzodiazepines, and so on, should be started without hesitation and lag, if required. Also, specific drug therapy, i.e., the muscle relaxant dantrolene and/or dopamine agonists (bromocriptine, amantadine) for NMS, and 5-HT receptor antagonists (cyproheptadine, methysergide) for serotonin syndrome, must be considered. However, it should be kept in mind that these psychopharmacological treatments have been reported anecdotally with controversial results, especially in the case of serotonin syndrome. As pointed by Gillman [21] and Boyer and Shannon [26], both bromocriptine and chlorpromazine should be avoided if the diagnosis is still uncertain, since the former may worsen serotonin syndrome and the latter is a dopamine antagonist that is contraindicated to NMS. Although Brimes *et al.* [120] mentioned the use of ziprasidone as a promising therapeutic option for the treatment of serotonin syndrome, this is not approved when considering its agonistic effect at 5-HT_{1A} receptors [121].

CONCLUDING REMARKS

With the increased prevalence of atypical antipsychotics and SSRIs in recent years, toxic encephalopathy with neuromuscular and autonomic symptoms indicative of the possibility of atypical NMS or serotonin toxicity may be frequently seen in clinical practices. According to the term “neuroleptic” malignant syndrome as well as the exclusion criteria of serotonin syndrome that a neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms [16,24], most cases who develop the clinical features common to NMS and serotonin toxicity in association with the treatment regimen including antipsychotic drugs have had a tendency to be diagnosed as NMS, but not as serotonin toxicity. However, there have recently

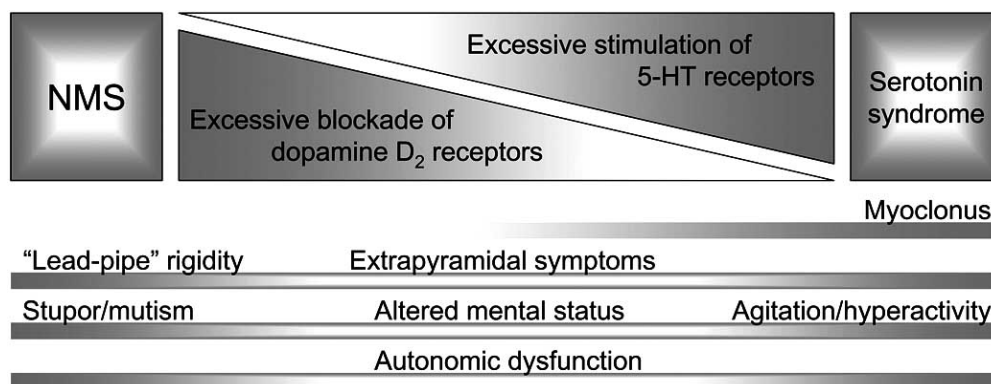


Fig. (3). The proposed pathophysiological background underlying the neurotoxic reaction to psychotropic drugs or drug combinations that have pharmacological potentiality to stimulate 5-HT receptors as well as to block dopamine receptors. Typical forms of NMS and serotonin syndrome exist as the ends of both pathophysiological processes. When both pathophysiological processes appear to be involved, physicians should try to evaluate to which extent each process contributes to the clinical features of the patients.

been several case reports where the diagnosis of serotonin toxicity or serotonin syndrome is given to the clinical symptoms subsequent to the treatment with atypical antipsychotics, e.g., risperidone [122-124], olanzapine [125-128], quetiapine [124,129], ziprasidone [130], and perospirone [131], prescribed in combination with other psychotropic drugs with serotomimetic properties, mostly SSRIs. In these case reports, the putative mechanisms underlying the development of serotonin syndrome associated with atypical antipsychotics are supposed to be ascribed to their potent 5-HT_{2A} receptor antagonism or to their pharmacokinetic interaction with coincidentally prescribed SSRIs through the common cytochrome P450 isoenzyme metabolism. However, as criticized by Isbister [132] and Isbister *et al.* [133], it may be questionable whether some of these cases are truly attributable to serotonin syndrome and whether atypical antipsychotics such as risperidone and olanzapine, that are potent 5-HT_{2A} antagonists without any direct serotomimetic activity, have a potentiality to cause serotonin toxicity. Nevertheless, apart from the cases of risperidone and olanzapine, the above-mentioned pharmacological properties of many atypical antipsychotics as partial 5-HT_{1A} receptor agonists may contribute to the development of serotonin toxicity associated with these atypical antipsychotics.

Our knowledge concerning the pharmacological and biochemical characteristics of psychotropic drugs is still incomplete. Even practitioners should be aware of the updated information provided by basic research. This would help the clinicians to treat their patients in a flexible and reasonable way to provide them with the most favorable and the least disadvantageous clinical outcome. The author hopes the consideration described in this review is of some help to the clinical psychiatrists who have diagnostic and therapeutic difficulties in managing the patients with NMS-like symptoms in relation to the psychotropic regimen including atypical antipsychotics.

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