Original Article

Knowledge, Attitude, and Practice (KAP) Study on Serotonin Syndrome Among Neuro Physicians

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Abstract

Background and Aims: Serotonin syndrome (SS) is a highly underdiagnosed drug-induced clinical syndrome. Under diagnosis is partly due to the unawareness of this syndrome by physicians. The aim of this study is to assess the knowledge, attitude and practice of SS among neuro physicians in India. **Methods:** A cross-sectional survey using a self-administered questionnaire was carried out among neuro physicians in India. Neuro physicians attending the various neurological conferences and meetings were approached to participate in the study. **Result:** A total of 150 neuro physicians responded to the survey. About 31% of participants correctly recognized the criteria for SS. Only 17% of the neuro physicians considered clonus as the most important feature in SS. Very few physicians correctly identified serotonergic agents causing serotonin syndrome. Similarly, a very low percentage of neuro physicians correctly identified the drugs used in the management of SS. Drugs used for the treatment of SS were incorrectly recognized as drugs causing SS. Clonus is the most specific feature for SS. However, examination for clonus is not a routine phenomenon in clinical practice among neuro physicians. **Conclusion:** This study shows great deficiencies in all domains of SS among neuro physicians. There is a need to make every doctor aware of SS by educational programs.

Keywords: Cyproheptadine, drug- toxicity, serotonin, serotonin syndrome

Introduction

Serotonin syndrome (SS) is a potentially life-threatening drug-induced syndrome caused by the excess intrasynaptic concentration of serotonin.[1] The incidence of SS has been increased in the recent past because of the widespread use of various serotonergic agents.[2] The rising incidence of cases of SS is a serious concern worldwide. Buckley *et al*. writes 'The steady increase in use of such drugs means all doctors need to be aware of what drugs increase serotonin and how to promptly recognize the syndrome….'.[3]

However, it is a highly underdiagnosed clinical syndrome. In one survey, done in the late 90s', 50 general practitioners (GPs) were asked about the serotonin syndrome. 85% of the responding doctors were unaware of the SS as a disease entity.[4] SS has protean manifestations and mimics a variety of medical conditions. Clinicians may dismiss mild SS unrelated to drug therapy.[1] A few proserotonergic agents are not marketed as serotonergic agents and physicians may not be aware of their property to cause SS.[3] Diagnosis of SS is purely clinical and it mainly depends on the demonstration of a few physical signs (clonus, hyperreflexia, tremor, hypertonia, etc.).[1,5] Such examinations are often omitted by physicians for nonspecific symptoms.[6] There hence seems to be some gaps in knowledge, attitude and practice about serotonin syndrome. There is a need to make every physician aware of this potentially fatal clinical condition. Therefore, the identification of deficiencies in physicians' knowledge, attitudes, and practices of SS may be the first step in this regard. The clinical features of SS include a triad of neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status.[1] Neuro physicians are hence more likely to encounter the cases of SS. Therefore, we decided Knowledge, Attitude, and Practice (KAP) survey for serotonin syndrome among neuro physicians.

Methods

This cross-sectional questionnaire-based study was done by a convenient sample method between September 2018 and July 2019. Neuro physicians attending the various neurological conferences and meetings were approached to participate in the study. The inclusion criteria were as: (i) neuro physicians having a postgraduate degree in neurology, (ii) willing to participate in the study, and (iii) ready to answer the questionnaires on the spot. Training neurologists (students and residents) were excluded from the study. All questionnaires were distributed personally by one of the authors on the sites. Participants were requested to respond immediately.

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Those who did not return the questionnaire immediately were excluded from the study. Participants were explained about the purpose and methods of the survey.

The questionnaire was developed by the investigators and validated on 20 randomly selected physicians to ensure accuracy and remove the ambiguity of the questions. It contains 10 multiple-choice questions. The responded were asked to mark the correct response to each question. Four questions were related to clinical features or Hunter criteria for serotonin syndrome. These questions had one correct answer. Three questions were targeting to identify serotonergic drugs. These questions had multiple correct answers.

Clonus is considered as the most important physical sign in establishing the diagnosis of SS. A diagnosis of SS cannot be made without examining the patients for clonus. Therefore, two questions were related to clonus. One question was related to the therapy of SS.

In such type of survey (involving super-specialty physicians), maintaining confidentiality was very important to increase the participation and response rate. We did not collect personal or identifiable data to ensure confidentiality. Written consent was not taken as the return of the questionnaires implied willingness to participate. The Institutional Ethic Committee (IEC) approved the study protocol. We used Microsoft Excel and Graph Pad for statistical analysis. The responses were summarized as number and percentage. The responses between the groups of participants were compared using Fisher's exact test. All *P* values were two-tailed, and a *P* value < 0.05 was considered as statistically significant. All data generated and analyzed during this study are included in this article.

Result

A total of 150 neuro physicians participated in the study. Table 1 shows the responses related to knowledge, attitude, and practice of SS among neuro physicians. Question number 1-4 were related to diagnosis and clinical features. Sixty-one percent participant had seen cases with SS in their clinical practice. However, only 31% participants correctly recognized the criteria for SS (Hunter criteria). Clonus is strongly associated with serotonin toxicity, and Hunter Serotonin Toxicity Criteria consider clonus as the most important clinical sign. However, on responding to the most specific feature for SS, only 17% neuro physicians marked clonus as the most important feature in SS. When asked to indicate the autonomic feature mentioned in the Hunter criteria, only 38% participants correctly recognized diaphoresis.

Question number 5-7 had multiple drug options. Participants were asked to recognize the serotonergic agents. There were a total of 15 drugs in these 3 questions; 9 drugs were classified as proserotonergic agents and another 6 were non-serotonergic drugs. The response is summarized separately in Tables 2 and 3. Table 2 shows the response rate for serotonergic agents. This list largely includes drugs that have proserotonergic effects, but are not marketed as serotonergic agents. The correct response for these drugs were as follows: Ondansetron (8%), lithium (9%), ginseng (11%), dextromethorphan (18%), tramadol (21%), linezolid (25%), venlafaxine (27%), chlorpheniramine (37%) and sodium valproate (47%). Table 3 shows non-serotonergic agents which were incorrectly recognized as drugs causing serotonin syndrome. Cyproheptadine is the drug of choice for SS. However, 17% recognized it as a serotonergic agent. Chlorpromazine is another drug found to be effective in patients with SS. However, 73% of the participants labeled chlorpromazine as a drug causing SS. Olanzapine is also used for the treatment of SS. About 60% participants labeled olanzapine as a serotonergic agent. Trihexyphenidyl (36%) was the most common response when asked about the recommended therapy for SS. Only 24% correctly recognized that cyproheptadine is the main recommended therapy for SS. A few participants opted for two options.

Clonus is the central feature in the Hunter criteria of SS. However, examination for clonus in clinical practice is not a routine phenomenon. Hence, we wanted to know how frequently neuro physicians look for clonus in their routine clinical practice. For that, we asked when you last examined for clonus in any patients in outpatient clinic and intensive care unit (ICU) setting. Only 17% participants admitted that they have looked for clonus in the ICU in the last month. About 60% respondents have not examined for clonus in ICU patients in the last 3 months. Even in the outpatient clinic, only 34% have looked for clonus in the last one month.

Table 4 compares the different aspects of knowledge, attitude, and practice of SS between neuro physicians who have seen cases of SS and those who have never seen cases of SS in the past. There was no significant difference between groups in any domains. Among 92 physicians who had diagnosed SS in the past, only one-third were aware of the Hunter criteria, and only 20% recognized clonus as the most specific feature of SS. About two-third participants in both groups considered olanzapine and chlorpromazine as a serotonergic agent.

Discussion

This study noted significant deficiencies in the knowledge, attitudes, and practices among neuro physicians on SS. These deficiencies could be the reasons for the under diagnosis of SS. A diagnosis of SS is purely clinical, and laboratory tests are done to exclude other secondary causes. A few diagnostic criteria have been suggested for SS. The first criteria (Sternbach's criteria) were introduced in 1991.[7] However, it was never validated. The most recent and widely used criteria for SS is Hunter Serotonin Toxicity Criteria, which have a sensitivity of 84% and specificity of 97%. This criteria is very simple that includes a few clinical symptoms and a few physical signs.[5] However, only 31% participants correctly recognized Hunter Criteria as a criteria for SS. Even the physicians who made a diagnosis of SS in the past were not aware of Hunter criteria.

Table 1: Responses of neuro physicians to knowledge, attitude and practice questionnaire related to serotonin syndrome

Item no.	Questions	Response *n* (%)
1	Have you ever diagnosed a case of serotonin syndrome?	
	Yes	92 (61)
	No	58 (39)
2	Which one is the criteria for serotonin syndrome?	
	(i) Caplan's criteria	26 (21)
	(ii) Engel's criteria	32 (21)
	iii) Hunter's criteria	46 (31)
	(iv) Newman's criteria	21 (14)
	(v) Purdy's criteria	17 (11)
	(vi) Did not respond	8 (5)
3	Which is the most specific feature for the diagnosis of serotonin syndrome	
	(i) Bradykinesia	32 (21)
	(ii) Myoclonus	32 (21)
	(iii) Clonus	26 (17)
	(iv) Extensor planter	22 (15)
	(v) Catatonia	19 (13)
	(vi) Did not respond	19 (13)
4	Autonomic feature included in the criteria of serotonin syndrome	
	(i) Orthostatic hypotension	23 (15)
	(ii) Diaphoresis	57 (38)
	iii) Miosis	42 (28)
	(iv) Sexual dysfunctions	4 (3)
	(v) Decreased bowel sound	4 (3)
	(vi) Did not respond	20 (13)
5	Kindly tick the drug (s) that may cause serotonin syndrome (more than one answer may be correct)	
	(i) Tramadol	31 (21)
	(ii) Olanzapine	90 (60)
	(iii) Chlorpromazine	109 (73)
	(iv) Ginseng	17 (11)
	(v) Cyproheptadine	26 (17)
6	Kindly tick the drug (s) that may cause serotonin syndrome (more than one answer may be correct)	
	(i) Lithium	14 (9)
	(ii) Chlorpheniramine	56 (37)
	(iii) Sodium valproate	70 (47)
	(iv) Topiramate	52 (35)
	(v) Ondansetron	12 (8)
7	Kindly tick the drug (s) that may cause serotonin syndrome (more than one answer may be correct)	
	(i) Linezolid	37 (25
	(ii) Vancomycin	34 (23)
	(iii) Rifampicin	44 (29)
	(iv) Venlafaxine	41 (27)
	(v) Dextromethorphan	27 (18)
8	Which is the recommended therapy for Serotonin syndrome?	
	(i) Bromocriptine	22 (15)
	(ii) Trihexyphenidyl	54 (36)
	(iii) Dopamine agonist	29 (19)
	(iv) Dantrolene	35 (23)
	(v) Cyproheptadine	36 (24)
9	When did you last time examine for clonus in outpatient clinic patients	
	(i) In this month only	51 (34)
	(ii) One month back	35 (23)
	(iii) 3 months back	32 (21)
	(iv) 6 months back	24 (16)
	(v) 12 months back	4 (3)

Contd...

Table 1: Contd...

Item no.	Questions	Response *n* (%)
	(vi) can't remember	4 (3)
10	When did you last time examine for clonus in Intensive Care Unit patients	
	(i) In this month only	25 (17)
	(ii) One month back	35 (23)
	(iii) 3 months back	58 (39)
	(iv) 6 months back	25 (27)
	(v) 12 months back	3 (2)
	(vi) can't remember	4 (3)

Table 2: Serotonergic agents- Correctly recognized as drugs causing SS

Serotonergic drugs	Correct response, *n* (%)
Ondansetron	12 (8)
Lithium	14 (9)
Ginseng	17 (11)
Dextromethorphan	27 (18)
Tramadol	31 (21)
Linezolid	37 (25)
Venlafaxine	41 (27)
Chlorpheniramine	56 (37)
Sodium valproate	70 (47)

Table 3: Non-serotonergic agents wrongly recognizing as serotonergic agents

Non Serotonergic drugs	Wrong response, *n* (%)
Chlorpromazine	109 (73)
Olanzapine	90 (60)
Topiramate	52 (35)
Rifampicin	44 (29)
Vancomycin	34 (23)
Cyproheptadine	26 (17)

Clinically, SS is characterized by a triad of increased neuromuscular activity, autonomic hyperactivity, and impaired mental status. This triad includes a wide range of clinical symptoms and physical signs.[2] However, Hunter criteria includes only the following 7 clinical features: Tremor, fever, diaphoresis, agitation, clonus (spontaneous, induced or ocular), hyperreflexia, and hypertonia or rigidity. We noted great deficiencies in knowledge about the Hunter criteria. Clonus is the most specific for SS. However, only 17% were aware of its clinical significance in diagnosing SS. Only 38% recognized that diaphoresis is a part of the Hunter criteria.

SS is a drug-induced clinical phenomenon. More than 50 drugs have been identified in the literature that induce or contribute in the pathogenesis of SS.[1,5] There are several mechanisms to increase serotonin concentration at the synapses. The 5-HT2A receptor is the main receptor implicated in the pathogenesis of SS. However, the 5-HT1A receptor may also contribute substantially.[1] Typically, SS is described in relation to Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants which decrease serotonin reuptake.

However, there are several other mechanisms to increase serotonin concentration at synapses: Decreasing serotonin breakdown (Monoamine oxidase inhibitors and Linezolid), increasing serotonin precursors or agonists (L-tryptophan, buspirone, etc.), and increasing serotonin release (amphetamine, cocaine, lithium, etc).[8] There are seven families of serotonin (5-HT1 to 5-HT7). Blockade of other serotonin receptors increases synaptic concentration of serotonin for 5-HT2A and 5 HT1A. Ondansetron is a 5-HT3 antagonist. Blockade of the 5-HT3 receptor increases synaptic concentration of serotonin at the unblocked 5-HT2A and 5-HT1A.[9] Olanzapine cause blockade of 5-HT2 and 5-HT3 receptors. So, largely olanzapine is used as a treatment of SS. But, olanzapine may precipitate SS in patients who are on mirtazapine by activating 5-HT1.[10] So, there are multiple mechanisms to induce SS. However, several drugs with serotonergic properties are not classified or marketed as serotonergic agents (such as ondansetron, tramadol, dextromethorphan, and linezolid). A large number of participants did not recognize these drugs as serotonergic agents. Tramadol is one of the common drugs causing SS. It was the most common drugs in the Prakash *et al*. series of 45 Patients with SS.[2] It was the third most common drug in Abadie *et al*. observations.[11] However, only 21% participants recognized its proserotonergic property. Ondansetron is one of the commonly used drugs in the clinical practice. There are several case reports of SS induced by ondansetron.[2] However, only 8% participant recognized it as a serotonergic agent. The serotonergic effect of lithium was recognized by only 9% neuro physicians.

The management of SS depends on the severity and associated clinical features, and it includes discontinuation of serotonergic agents, supportive care, and a 5-HT 2A–antagonist. Cyproheptadine is the most widely used 5-HT 2A–antagonist for SS.[1] However, only 24% correctly recognized this fact. Intravenous chlorpromazine is the preferred treatment in severe serotonin toxicity.[1,12] But, more than 73% participants incorrectly recognized it as a drug causing SS. Atypical antipsychotics with predominate HT 2A–antagonist (Olanzapine and risperidone) may also be beneficial in serotonin syndrome.[1] However, 60% respondents considered olanzapine as a drug

Table 4: A comparison between neuro physicians who have made a diagnosis of SS earlier to who had never made a diagnosis of SS

	Physicians who diagnosed SS (*n*-92) (*n*, %)	Physicians who never diagnosed SS (*n*-58) (*n*, %)	*P*
Knowing Facts about clinical features and criteria			
Know Hunter criteria	31 (34)	15 (26)	0.36
Clonus- most specific	18 (20)	8 (14)	0.50
Diaphoresis - most specific autonomic features	34 (37)	23 (40)	0.86
Recognizing serotonergic drugs			
Tramadol	23 (25)	8 (14)	0.14
Ginseng	7 (8)	10 (17)	0.11
Lithium	10 (11)	4 (7)	0.39
Chlorpheniramine	36 (39)	20 (34)	0.60
Sodium valproate	45 (49)	25 (43)	0.50
Ondansetron	7 (8)	5 (9)	1.00
Linezolid	27 (29)	10 (17)	0.12
Venlafaxine	25 (27)	16 (28)	1.00
Dextromethorphan	19 (21)	8 (14)	0.38
Non serotonergic drugs recognizing as serotonergic drugs			
Olanzapine	57 (62)	33 (57)	0.60
Chlorpromazine	71 (77)	38 (66)	0.13
Cyproheptadine	13 (14)	12 (21)	0.36
Topiramate	28 (30)	24 (41)	0.21
Vancomycin	23 (25)	11 (19)	0.42
Rifampicin	30 (33)	14 (24)	0.70
Recognizing drug of choice			
Cyproheptadine	26 (28)	10 (17)	0.16

causing SS. Bromocriptine, dantrolene, and propranolol are not recommended in SS. Bromocriptine and dantrolene may exacerbate the serotonin syndrome.[1] However, a large number of respondents considered bromocriptine and dantrolene as a therapeutic option for SS.

Our study demonstrated that examination for clonus is not a regular phenomenon in both the outpatient clinic and intensive care unit (ICU) setting. In Ewijk *et al*. observations, 72% patients with delirium in ICU were on serotonergic drugs, and 16% fulfilled the Hunter serotonin toxicity criteria.[13] It highlights the need of examination for clonus in ICU patients. Cases of SS have been described in all clinical settings. SS may present in many different ways.[2] So, there is a need to make physicians aware of the diagnostic value of clonus.

This study shows great deficiencies in all domains of SS among neuro physicians. Only a minority of the participants were aware of the specific clinical features and criteria of SS. Only a few recognized clonus as a most specific feature of SS. Very few physicians correctly identified serotonergic agents causing serotonin syndrome. Similarly, a very low percentage of neuro physicians correctly identified the drug used in SS. Drugs used in the treatment of SS (such as cyproheptadine, chlorpromazine, and olanzapine) were incorrectly recognized as drugs causing SS. Moreover, examination for clonus is not a routine phenomenon. These all may be the reasons for the under diagnosis of SS. We didn't find any significant differences between neuro physicians who have seen cases of SS earlier to those who never saw such cases in the past. Hence, gaps in knowledge were uniform among neuro-physicians.

Incidence of SS is not rare. A large number of drugs may cause SS. It may occur in all clinical settings. Moreover, it is potentially a life-threatening condition. That's why it is suggested that every doctor should be aware of SS.[3] Because of its clinical presentation (cognitive impairment and neuromuscular abnormalities), neuro physicians are supposed to be more familiar with SS than others. However, the present KAP study on SS among neuro physicians was not encouraging. It will be interesting to do a similar study on the expert of other medical fields.

Our study indicates that a lot of things are to be done to make every physician aware of SS. SS should be the part of educational intervention or program. Besides neurologists, psychiatrists and physicians working in ICU are more likely to encounter the cases of SS. There are several case reports of SS after surgery or anesthesia. Physicians working in this field should also be aware of SS.

Limitation

There were several problems in doing a KAP study among doctors who are supposed to be experts on that topic. To encourage the participation rate, we didn't take any personal details (age, years of experience, etc.) and the number of

questions was kept limited. The study was done on a convenient sample. So, the results may not be generalized as the study sample may not be the true representative sample of neuro physicians. In addition, there could be a responder bias as only respondents who have a better knowledge of serotonin syndrome may have participated. As the number of questions was very limited, the knowledge, attitude, and practice of the participation for SS cannot be fully determined. Despite these limitations, we hope that our observations will serve as a catalyst to increase the awareness of SS among all doctors around the world.

Conclusion

The present KAP-survey on SS has demonstrated great deficiencies in all domains of SS. There is a need to make physicians aware and familiar with all aspects of SS.

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Declaration of patient consent

The authors certify that they have obtained verbal consents from the participants. Written consent was not taken as the return of the questionnaires implied willingness to participate.

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Conflicts of interest

There are no conflicts of interest.

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