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The serotonin syndrome scale: first results on validity

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Abstract As a modification of the diagnostic criteria of the serotonin syndrome proposed by Sternbach, we developed the Serotonin syndrome scale for the operationalized assessment of both the presence and the severity of the core symptoms of the serotonin syndrome. In a first study on the validity of this scale, the relationships between the serotonin syndrome score (SSS) and both the paroxetine plasma levels (n = 42) and the loudness dependence of the auditory evoked potentials (LDAEP; n = 24) were investigated in depressed patients treated with paroxetine. A strong LDAEP is supposed to indicate low central serotonergic neurotransmission, and vice versa. The SSS was positively related to paroxetine plasma levels and negatively to the LDAEP. Both results support the validity of the serotonin syndrome scale. Using a SSS > 6 as diagnostic criterion, mild serotonin syndromes were diagnosed in 5 of our 42 patients. The Serotonin syndrome scale may become a useful tool for clinicians and scientists dealing with the serotonin syndrome.

Key words Serotonin syndrome · Paroxetine · Plasma levels · SSRI · Auditory evoked potentials

Introduction

Serotonergic drugs and especially selective serotonin reuptake inhibitors (SSRI) are increasingly used for the pharmacotherapy of patients with depression, obsessive-compulsive disorder and other psychiatric disorders. Therefore, an increased incidence of serotonin-related side effects has to be expected, the serotonin syndrome representing its severest form (reviewed by Sternbach 1991; Lejoyeux et al. 1994). This potentially fatal syndrome can develop when drugs with different serotonin agonistic effects are combined (e.g. monaminoxidase inhibitors and SSRI), but also under a monotherapy with a serotonin agonist (Sporer 1995; Fischer 1995). An enhanced activity of both the central and peripheral serotonin systems are supposed to explain the clinical symptoms (Brown et al. 1996). Whereas a full serotonin syndrome is a rare event, the incidence of milder forms is unknown. It is not always easy to recognize these milder forms and to delineate them from for example, depressive syndromes with agitation, neuroleptic malignant syndromes or anticholinergic delirant syndromes in comedicated patients. At present, it remains unclear to what extent these different syndromes overlap not only with respect to their symptomatology but also with respect to pathophysiological mechanisms involved. Reliable criteria for the diagnosis of the serotonin syndrome are needed as a basis for research in this area and as a help for clinical diagnosis. Based on a review of 38 case reports, the following criteria have been proposed by Sternbach (1991):

1. 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: (a) mental state changes (confusion, hypomania); (b) agitation; (c) myoclonus; (d) hyperreflexia; (e) diaphoresis; (f) shivering; (g) tremor; (h) diarrhea; (i) incoordination; (j) fever.

2. Other aetiologies have been ruled out.

3. A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.

In many later case reports the serotonin syndrome has been diagnosed referring to these criteria. However, a shortcoming of these criteria is the fact that the severity of the different symptoms is not taken into account. It is not unusual to find mild tremor, agitation and diaphoresis in depressed patients treated, for example, with tricyclic antidepressants. Although three of the ten symptoms may be present in such cases, it would not be justified to diagnose a serotonin syndrome in all these patients. On the other

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hand, the serotonin syndrome may exist in different degrees of severity. Although most authors denote with "serotonin syndrome" an acute and clinically severe syndrome which occurs in close temporal connection with the beginning or the increase in dosage of serotonergic drugs, there may be a continuum to mild and subacute forms. Such forms have been described by Lejoyeux et al. (1993) in a prospective study on serotonin-related symptoms in depressed inpatients. It would be of clinical importance to recognize already such mild forms in order to prevent a further deterioration and a confusion with depressive symptoms.

For the assessment of both full-blown and subacute forms of the serotonin syndrome we modified Sternbach's diagnostic criteria and developed a scale for the operationalized assessment of the presence and the severity of the serotonin syndrome. This scale includes most of the items proposed by Sternbach. Instead of the related items "mental status changes (confusion, hypomania)" and "incoordination" as proposed by Sternbach, we included "disorders of orientation" and "dizziness". "Mental status changes (confusion, hypomania)" included in Sternbach's list is difficult to assess because independent symptoms, such as confusion and hypomania, are linked together. Furthermore, the item "agitation", which is included in Sternbach's as well as in our list, already covers aspects of hypomania. We have included "disorders of orientation" because this item is easier to operationalize than "mental status changes". Instead of "shivering", "fever" and "diaphoresis" we included only "fever" and "diaphoresis". We omitted the item "shivering" because there are already two other items related to body temperature regulation. Furthermore, "shivering" is a relatively rare symptom of the serotonin syndrome (see e.g. Sporer 1995; Sternbach 1991) and as a mainly subjective item it cannot easily be operationalized. The proposed scale consists of nine items rated from 0 = not present to 3 = severe. The Serotonin Syndrome Score (SSS) is the sum score of these items. A serotonin syndrome is supposed to be present when the SSS is greater than six. This cut-off point was chosen, because a score greater six can only be obtained when at least three different symptoms are present, in line with Sternbach's criteria. Nausea and headache, which are frequently reported in the first days after starting medication, are not considered to be core symptoms of the serotonin syndrome and are not included in the scale. (A German version of the scale is available upon request.)

Within a naturalistic setting we performed a study on depressed inpatients treated with paroxetine. Our aim was to give first evidence for the validity of this SSS by investigating three aspects:

1. The relationship between the SSS and paroxetine plasma levels. A positive correlation has to be expected.

2. The relationship between the SSS and the loudness dependence of the auditory evoked potentials (LDAEP). This relationship is of interest because theoretical, clinical and preclinical arguments indicate that a strong LDAEP is related to low central serotonergic function (Hegerl and Juckel 1993; Hegerl et al. 1994, 1996). Recent animal experiments lend further support to the notion that the LDAEP is one of the best available indicators of central serotonergic function in humans (Juckel et al. 1997). If the SSS reflects a state of enhanced central serotonergic neurotransmission, a negative correlation to the LDAEP has to be expected.

3. The relationship between the SSS and the clinical severity of the serotonin syndrome. A score greater six is supposed to correspond to a manifest serotonin syndrome.

Materials and methods

Subjects and procedure

All inpatients with a depressive syndrome who were treated with paroxetine were included in the study, when the responsible clinician decided to measure the paroxetine plasma levels. Reasons for this decision were for example, nonresponse, possible serotonin-related side effects, comedications (e.g. carbamazepine), comorbidity or only routine plasma level monitoring after 4 weeks of antidepressant treatment. Blood was drawn before the morning dose (20–24 h after last oral paroxetine application).

Patients were diagnosed according to ICD-10. Most of the patients had a depressive episode within a unipolar affective disorder (see Table 2). Diagnoses were made by an experienced psychiatrist together with a senior psychiatrist. On the same day, the patients were clinically examined and serotonin-related side effects were scored using the operationalized criteria of the serotonin syndrome scale (Table 1). Depression was rated with the Hamilton Depression Rating Scale (HDRS, 21 items). These examinations and ratings were performed in most cases by the physician responsible for the patient at the ward. Forty-two patients were recruited. In 3 of these patients the HDRS scores were missing. On the same day, in 31 of these patients additionally the LDAEP was assessed. Seven patients had to be excluded from the evaluation mainly because of high rates of ocular artefacts.

Method for the determination of paroxetine

Paroxetine was measured with high-performance liquid chromatography (HPLC) with native fluorescence detection. For paroxetine one method using derivatisation and fluorescence detection has been published (Brett et al. 1987). For routine plasma monitoring of paroxetine no derivatisation is necessary because of the high sensitivity and selectivity of the naturally occurring fluorescence (H.-J. Kuss et al. unpublished data).

Extraction

In a polypropylene vial 1 ml plasma were added to 300 ng trimipramine in 100 µl diluted phosphoric acid for internal standardisation and 1 ml sodiumhydrogencarbonate solution (pH = 10.5). The mixture is extracted with 6 ml hexane containing 1.5% amylalcohol. The hexane is transferred into another polypropylene vial and the antidepresssants are back extracted into 300 µl diluted phosphoric acid. Of the aqueous phase 150 µl are injected in the HPLC system.

Chromatography

The HPLC system consists of a LC-9A pump, an autoinjector SIL-9A and integration system Class-LC10 (Shimadzu) connected to a fluorescence monitor (excitation at 254 nm and emission between 300 and 400 nm; LDC). Separation is done on a 250– × 4-mm Su-

Table 1 Serotonin syndrome scale

Agitation (motoric restlessness also akathisia)
0 = None
1 = slight and intermittent
2 = moderate (unrest sitting)
3 = severe and permanent/long-lasting sitting is nearly impossible, patient always feels restless

Disorders of orientation
Orientation: according to time, place, person and situation. The most severe expression is accounted. If there is more than one quality significantly impaired, the whole item should be scored with 3

Myoclonus (sudden clinic jerks of some muscles without or with only little movement effect, "sleeping jerks" should be not scored)
0 = no myocloni
1 = patient reports some short episodes
2 = patient reports repeated episodes; isolated myocloni are visible
3 = permanent, visible myocloni

Hyperreflexia
0 = no hyperreflexia
1 = hyperreflexia with normal reflexogenic zone
2 = hyperreflexia with enlarged reflexogenic zone, exhaustible cloni
3 = hyperreflexia enlarged reflexogenic zone, non-exhaustible cloni

Tremor
0 = no tremor
1 = tremor with small amplitude, functioning is not impaired
2 = tremor with a significant amplitude, functioning (to hold a cup, writing, etc.) is moderately impaired
3 = tremor with a high amplitude; functioning is severely impaired

Dizziness (subjective feeling)
0 = None
1 = slight and intermittent feeling of dizziness
2 = patient feels dizzy most of the time, functioning (moving, standing) is not impaired
3 = patient always feels dizzy; functioning (moving, standing) is affected

Hyperthermia (sublingual)
0 = < 37 °C
1 = 37–37.9 °C
2 = 38–38.9 °C
3 = ≥ 39 °C

Sweating (in rest with normal environmental temperature)
0 = no sweating
1 = subjective feeling of increased sweating
2 = moist skin, some beads of perspiration can be seen
3 = visible beads of perspiration with wet clothes or bedspread

Diarrhoea
0 = no diarrhoea
1 = feces with reduced consistence, but normal frequency
2 = liquid feces and/or frequency 1–3/day
3 = like 2 but frequency > 3/day

persphere Selected B 4 μ column. The mobile phase consists of a 35% acetonitrile/75% phosphate buffer (0.1 m, pH = 3 mixture. The limit of quantitation is 2 ng/ml. The coefficient of variation for the analysis using the internal standard method is not allowed to exceed 5%.

LDAEP method

After excluding major hearing deficits with an audiogram, recordings took place in a sound-attenuated and electrically shielded room adjacent to the recording apparatus. The subjects were seated in a slightly reclining chair with a headrest. Evoked responses were recorded using an electrode cap with 29 electrodes. Three additional electrodes were placed (1 nasion, 2 mastoids). Cz was used as reference. Fpz was used as ground. The impedance was below 10 kOhm for each electrode. During the 17-min recording, the subjects were asked to look at a fixation point at the wall in front of them, in order to reduce ocular artefacts. Sinus tones (1000 Hz, 30 ms duration with 10 ms rise and fall time, ISI randomized between 1800 and 2200 ms) of five intensities (60, 70, 80, 90 and 100 dB sound pressure level) were presented binaurally in pseudorandomized form by headphones. The sampling period reached from 200 ms prestimulus to 600 ms poststimulus. One hundred

Table 2 Comparison of the low– and high serotonin syndrome score (SSS) group. (From Hegerl et al. 1996)

	Low SSS (0–3)	High SSS (4–9)	*p*-value[a]
N	21	21	
Male/female	4/17	7/14	
Age (years)	56.3 ± 16.7	57.6 ± 16.8	n.s.
Diagnoses (no. of patients)			
Unipolar affective disorder	15	16	
Bipolar affective disorder	3	0	
Dysthymia	0	1	
Anxiety and depressive disorder	1	1	
Schizoaffective or schizophrenic disorder	2	3	
HDRS score (n = 39)	14.9 ± 8.1	21.1 ± 11.2	p = 0.06
Medication (mean ± sd)			
Oral paroxetine dose (mg/d)	32.9 ± 9.6	35.7 ± 7.5	n.s.
Comedication (no. of patients)			
Further antidepressants	2	3	
Neuroleptics	6	9	
Benzodiazepines	2	2	
Carbamazepine	0	3	
Lithium	4	8	
Internistic medication	7	11	
Paroxetine plasma level (ng/ml)	60.9 ± 34.5	106.5 ± 90.1	p = 0.04

[a] *t*-test (two-tailed)

sweeps were recorded for each intensity. Before averaging, the first five responses were excluded in order to reduce short-term habituation effects. Furthermore, for artefact suppression, all trials were automatically excluded from averaging, when the voltage exceeded ± 50 μV in any of the 31 channels at any point during the averaging period. For each subject the remaining sweeps were averaged separately for the five intensity levels.

Dipole source analysis of these potentials was performed using brain electrical source analysis (BESA; Scherg and Picton 1991) with the aim to separate N1/P2 subcomponents overlapping at the scalp. The averaged curves of each subject were entered into BESA, where data reduction, baseline correction, digital filtering (1–20 Hz) and transformation to average reference data took place. To obtain an optimal signal-to-noise ratio for the dipole source analysis, a grand average over all intensities and all subjects was calculated. Based on this grand average, a "basic dipole model" was computed for the latency range of the N1/P2 component (66,7–217 ms). The frontopolar (Fp1, Fp2) and the nasion electrodes were not considered in the fit procedure in order to reduce effects of ocular artefacts. As found in previous studies (Hegerl et al. 1994), the N1/P2 potentials recorded at the scalp were nearly completely explained by one *tangential dipole* and one *radial dipole* per hemisphere. The tangential dipole is located in the superior plane and is supposed to represent mainly activity of the primary auditory cortex. The radial dipole is supposed to represent activity of secondary auditory areas in the lateral temporal cortex (Hegerl et al. 1994, Scherg and Cramon 1990). In order to get the individual dipole configuration for every subject, the sweeps of all intensities of every subject were averaged. The "individual dipole model" was found by starting with the "basic dipole model" and adjusting individually the orientation and location of the tangential dipoles. The radial dipoles were not fitted concerning location and orientation because they explained only a small amount of variance and correspondingly showed higher variability.

The individual curves of each patient were calculated according to the "individual dipole model". This was done separately for the five stimulus intensities. No additional fitting of location or orientation was performed for the different stimulus intensities because changes in location or orientation would be confused with changes in dipole amplitude. The N1/P2 component of the individual dipole source potentials was measured as N1/P2-epoch-amplitude in the latency range of 66.7–233 ms. The loudness dependence of the N1/P2-epoch-amplitude (mean amplitude values of right and left tangential dipoles) was measured as the median-slope. The median-slope was calculated from the slopes of all possible straight lines (n = 10) connecting the five amplitude values within the amplitude/stimulus intensity function (μVeff/10 dB; Hegerl et al. 1994).

Statistics

Statistics were performed with SPSS. Patients were separated at the median into groups with high and low SSS. Group differences were tested using two-tailed *t*-tests for independent samples. Furthermore, Spearman correlations were calculated between the SSS and the paroxetine plasma levels or the LDAEP.

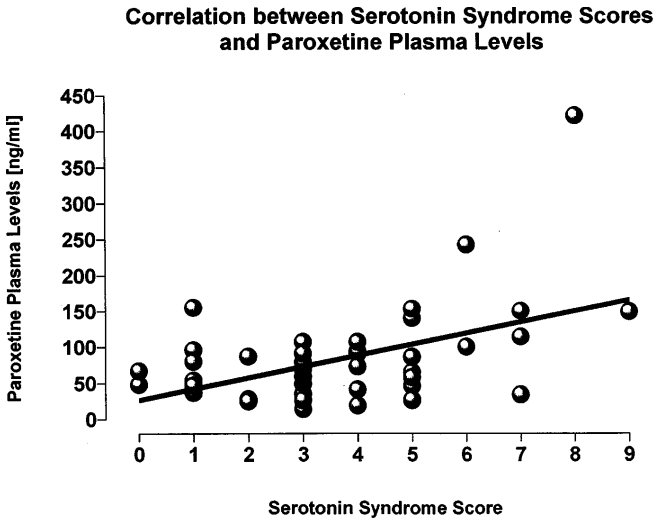

Fig. 1 Correlation between the serotonin syndrome score and paroxetine plasma levels

Table 3 Comparison of the low- and high-SSS group with loudness dependence of the auditory evoked potentials (LDAEP). (From Hegerl et al. 1996)

	Low SSS (0–3)	High SSS (4–9)	*p*-value[a]
N	11	13	
Male/female	2/9	5/8	
Age (years)	49.6 ± 16.9	55.9 ± 13.0	n.s.
Diagnoses (no. of patients)			
Unipolar affective disorder	8	10	
Bipolar affective disorder	1	0	
Anxiety and depressive disorder	1	0	
Schizoaffective or schizophrenic disorder	1	3	
HDRS score (mean ± sd)	13.8 ± 7.7	23.8 ± 11.6	0.02
Medication (mean ± sd)			
Oral paroxetine does (mg/d)	34.5 ± 11.3	36.9 ± 7.5	n.s.
Paroxetine plasma levels (ng/ml)	59.1 ± 29.0	76.1 ± 45.7	n.s.
Comedication (no. of patients)			
Further antidepressants	1	1	
Neuroleptics	3	6	
Benzodiazepines	1	2	
Carbamazepine	0	3	
Lithium	1	5	
Internistic medication	3	7	
LDAEP (μVeff/10 dB)	0.60 ± 0.16	0.38 ± 0.14	0.001

[a] *t*-test (two-tailed)

Results

In Table 2 patients split at the median SSS into a low-SSS group (SSS ≤ 3) and a high-SSS group (SSS > 3) are compared. The median was used for forming two groups and not the presence of a serotonin syndrome because only 5 patients had an SSS > 6. Both groups were not significantly different concerning age or daily paroxetine dose. The high-SSS group tended to be more depressed and had more comedication with psychotropic drugs. The paroxetine plasma levels were significantly higher in the high-SSS group.

Correspondingly, a significant correlation (Spearman correlation: $r = 0.32$, $p = 0.02$, $n = 42$) between the SSS and the paroxetine plasma levels was found (Fig. 1). This correlation also persists when HDRS score has been partialised out ($r = 0.33$, $p = 0.02$). The HDRS score was not related to the paroxetine plasma level ($r = 0.01$, $p = 0.48$; $n = 39$). There was no significant relationship between dosage and SSS (Spearman correlation: $r = 0.11$, $p = 0.47$; $n = 42$).

In Table 3 patients in which the LDAEP has been assessed are split into a low-SSS group (SSS from 0 to 3) and a high-SSS group (SSS from 4 to 9). Both groups were not significantly different concerning age or daily paroxetine dose. The high-SSS group had more comedication with psychotropic drugs and was more depressed. The LDAEP was significantly lower in the high-SSS group. Correspondingly, the SSS was negatively correlated with the LDAEP ($r = –0.64$, $P < 0.001$, $n = 24$; Fig. 2). When correlation between the SSS and the LDAEP is controlled for depression (HDRS score), it still remains significant ($r = –0.57$, $P = 0.002$). The HDRS score tended to correlate with the LDAEP ($r = 0.28$, $P = 0.09$; $n = 24$).

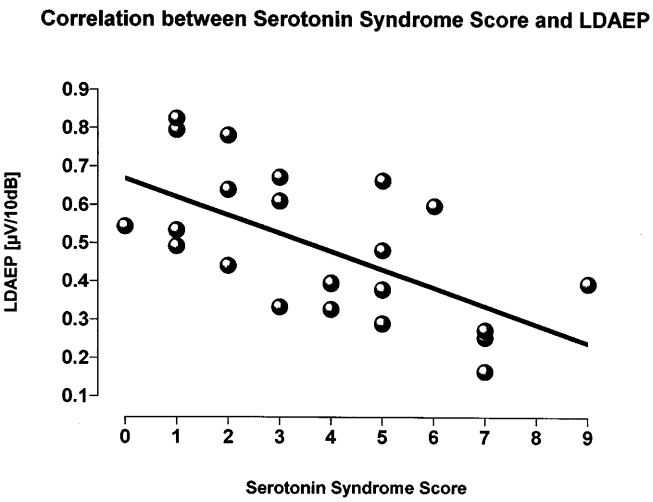

Fig. 2 Correlation between the serotonin syndrome score and the loudness dependence of the auditory evoked N1/P2 component (LDAEP; tangential dipoles)

Of the 42 patients, 26 suffered from agitation (mild: 17; moderate: 9), 2 from disorders of orientation (mild), 3 from myocloni (mild), 9 from hyperreflexia (mild: 6; moderate: 3), 26 from tremor (mild: 20; moderate: 5; severe: 1), 24 from dizziness (mild: 19; moderate: 5), 12 from hyperthermia (mild), 20 from sweating (mild: 14; moderate: 6) and 4 from diarrhoe (mild).

An SSS > 6 was found in 5 of the 42 patients. These patients are described in Table 4. One patient had ex-

Table 4 Patients with a serotonin syndrome score > 6

Patient no.	Age (years)	Gender	Diagnosis (ICD-10)	Serotonin syndrome score	Paroxetin treatment			Comedication	Hamilton Depression Rating Scale Score
					Duration (days)	Dosage (mg/day)	Plasma level (ng/ml)		
1	60	F	Major depression (F33.3)	7	51	50	114	Carbamazepine (200 mg/day) I-thyroxine (100 µg/day) Lorazepam (0.5 mg/day)	3
2	49	F	Schizoaffective disorder (F25.1)	7	16	30	34	Carbamazepine (600 mg/day) Perazine (200 mg/day)	38
3	74	F	Major depression (F33.2)	8	56	40	421	Lithium (18 mval/day) I-thyroxine (75 µg/day) Furosemide (20 mg/day)	No score available, not depressed according to the medical record
4	62	F	Major depression (F32.3)	7	16	30	150	Haloperidol (8mg/day) Dipiperone (40 mg/day) Allopurinal (300 mg/day)	33
5	33	M	Major depression (F33.1)	9	28	40	149	Lithium (24 mval/day) Propanolol (50 mg/day)	21

tremely high plasma levels (patient 3). This is not explained by pharmacokinetic interactions with comedication, because neither furosemide nor lithium are known to enhance paroxetine plasma levels (Van Harten 1993). However, two of them took lithium and two others took carbamazepine, which both can enhance the serotonergic neurotransmission. The involved mechanisms are discussed later. Two of these 5 patients with an SSS > 6 had a clinical relevant artherosclerosis. One of the 2 patients also suffered from a chronic obstructive pulmonary disease. The 3 other patients had no relevant somatic comorbidity. Myocloni and/or hyperreflexia were present in 3 (patients 1, 3 and 5) of the 5 patients. The neuroleptic dosage was stable for more than 4 weeks in patient 2 and was reduced (from dipiperone 3×40 to 1×40 mg) 3 days before the ratings in patient 4. Paroxetine medication had to be stopped or was reduced in 3 of the 5 patients. In none of these patients was thrombocytopaenia or leucopaenia found. When comparing the patients with an SSS > 6 ($n = 37$) to the 5 patients with an SSS > 6, the paroxetine plasma levels were higher in the high-SSS group (173.6 ± 146.1 vs 71.6 ± 46.5), but the difference did not reach significance. When considering patients with assessment of the LDAEP, those with an SSS > 6 ($n = 4$) had significantly lower LDAEP than the low-SSS group ($n = 20$; 0.27 ± 0.16 vs 0.53 ± 0.09; $p = 0.007$).

Discussion

The significant relationship found between the SSS and the paroxetine plasma levels supports the validity of the serotonin syndrome scale as reflecting serotonin-related side effects. To our knowledge, this is the first time a significant relationship could be demonstrated between SSRI plasma levels and serotonin-related side effects. This may be explained by the fact that the SSS takes into account the severity of the serotonin-related symptoms and includes symptoms such as hyperreflexia or myoclonus which often are not routinely monitored. Depressive symptoms and symptoms of a mild serotonin syndrome can overlap to some degree. There are common items, such as agitation or diarrhoea, and patients developing a serotonin syndrome may feel a worsening of their illness and may react with an increase in desperation and depression. Therefore, it is not surprising, that high-SSS patients tended to score higher on HDRS. The separation of depressive syndromes from mild serotonin syndromes is a difficult task, even for experienced clinicians. It is significant, however, that the SSS, but not the HDRS scores, showed a significant correlation to plasma levels. This indicates that the relationship between SSS and plasma levels is not mediated by depressive symptoms.

The clear relationship between the SSS and LDAEP additionally supports the validity of the serotonin syn-

drome scale as a tool to assess serotonin-related side effects. High-SSS patients have a low LDAEP indicating a strong central serotonergic neurotransmission. This relationship also does not seem to be mediated by depressive symptomatology, because only a week relationship is found between LDAEP and the HDRS score. The value of the LDAEP as an indicator of central serotonergic aspects is supported by several arguments, such as the high serotonergic innervation of the primary sensory cortices, the robust relationships between this parameter and serotonin-related personality traits, the effects of serotonin agonists on sensory evoked potentials, or the correlations between 5-HIAA levels in CSF and the intensity dependence of sensory evoked potentials (Hegerl and Juckel 1993; Hegerl et al. 1991, 1996). Further support is provided by recent animal experiments: systemic application of the 5-HT2 antagonist ketanserin and the 5-HT1a agonist 8-OH-DPAT as well as the modulation of the firing rate of serotonergic neurons by local application of 5-HT1a antagonist spiperone and 5-HT1a-agonist 8-OH-DPAT in the raphe nuclei in cats, affect the loudness dependence of the auditory evoked response of the primary auditory cortex in the expected manner: an increase of serotonergic function was followed by a decrease of the loudness dependence, and vice versa (Juckel et al. 1997). Despite this converging evidence for a relationship between serotonin and LDAEP, only a relative specificity of the relationship between LDAEP and central serotonergic function can be expected because of the close interactions between the different neurochemical systems. The low dopaminergic and noradrenergic innervation of the primary auditory cortex suggest that these systems play only a minor role in the modulation of sensory processing in auditory cortices, whereas the cholinergic system could be more involved (Juckel et al. 1997). Despite these limitations, the LDAEP is one of best available indicators of central serotonergic function in humans. Other possible indicators, such as biochemical peripheral parameters (Murphy 1990), have only a questionable validity. Taking 5-HIAA in the cerebrospinal for example, the relationship between this parameter and functional aspects of central serotonergic neurotransmission is not clear (Trulson 1985; Bacopoulos et al. 1979; Auerbach et al. 1989). Other parameters, such as serotonin transport in platelets, reflect only one of many subfunctions of serotonergic neurons, not allowing conclusions about central serotonergic net effects (Moret and Briley 1991). In 5 of 42 patients an SSS > 6 was found. Two of these patients were comedicated with neuroleptics. In line with Sternbach's (1991) criteria, a serotonin syndrome cannot be diagnosed when a neuroleptic had been started or increased in dosage prior to the onset of the syndrome. In such cases a malignant neuroleptic syndrome has to be considered as differential diagnosis. In our patients, however, the neuroleptic dosage had been stable for more than 4 weeks or had been reduced 3 days before the ratings (Table 4). Although minor effects of neuroleptic side effects on SSS cannot be excluded, it is unlikely that a malignant neuroleptic syndrome explains the high SSS in these patients. Therefore, the criteria for the diagnosis of a serotonin syndrome were present in 5 of the 42 patients (12%). This high rate was obtained, although our diagnostic criteria were more strict than those proposed by Sternbach (1991). For example, according to our criteria three symptoms with moderate severity (SSS = 6) would not be sufficient to reach the cutoff score of 7. This high rate of serotonin syndromes seems to be in contrast with the view that a serotonin syndrome is a rare event. However, when including not only severe but also mild and subacute forms, our findings correspond to those reported by Lejoyeux et al. (1993). Within a prospective study, this research group diagnosed a serotonin syndrome in 25% of their patients during parenteral monotherapy with clomipramine. As in our study, most of these serotonin syndromes were mild, not requiring discontinuation of medication. In our study, paroxetine medication was stopped or reduced in 3 of 5 patients. Furthermore, the high rate of serotonin syndromes in our study is explained in part by the naturalistic setting of our study. Paroxetine plasma levels were measured in some patients because a serotonin syndrome was suspected by the clinician.

Comorbidity can be a risk factor for the development of a serotonin syndrome. For example, serum 5-HT is inactivated by pulmonary and vascular endothelial MAO-A, hepatic inactivation and cellular reuptake. Dysfunction of vascular or pulmonary endothelium, atherosclerosis, hypertension and hypercholesterinaemia are all associated with a reduction in endothelial MAO-A activity and lead consequently to higher serum 5-HT levels. Since the serotonin syndrome reflects not only a central nervous, but also a peripheral, hyperserotonergic state, these conditions may be possible risk factors for the development of a serotonin syndrome (Brown et al. 1996). It is interesting that 2 of our 5 patients with an SSS > 6 had a clinical relevant artherosclerosis. One of the 2 patients also suffered from a chronic obstructive pulmonary disease. From the 3 other patients with an SSS > 6 no relevant somatic comorbidity is known.

Because of the depressive symptomatology, the comedication and the only mild symptomatology, the diagnosis of a serotonin syndrome remains somewhat uncertain in our 5 patients with an SSS > 6. However, evidence in favour of correct diagnoses is provided not only by the symptom clusters, but also by the fact that 4 of these 5 patients had high paroxetine plasma levels (> 100 ng/ml), and that 4 had a comedication with lithium or carbamazepine. Lithium has serotonergic effects and may have enhanced the serotonin agonistic effects of paroxetine. Serotonin syndromes with the combination of SSRI and lithium have been described (Kojima et al. 1993; Muly et al. 1993; Öhman and Spigset 1993; Sobanski et al. 1996). With regard to carbamazepine, it is of interest that this drug has been found to increase whole and free plasma concentrations of tryptophan and to decrease bound-to-free plasma tryptophan ratios. Furthermore, the tryptophan concentrations were found to rise with increasing carbamazepine concentrations (Pratt et al. 1984). Since tryptophan is the precursor of serotonin, carbamazepine

may add to the serotonin agonistic effects of paroxetine. The possible serotonin agonistic effect of carbamazepine is further supported by the finding that carbamazepine increases serotonin-mediated neuroendocrine responses in healthy subjects (Elphick et al. 1990). In line with this reasoning, a serotonin syndrome with the combination of SSRI and carbamazepine has been described (Dursun et al. 1993).

The clinical data show that using an SSS > 6 as cutoff point, patients with mild and subacute forms of the serotonin syndrome will be included in the serotonin syndrome group. Such a broad serotonin syndrome concept may be clinically useful for early detection of serotonergic reactions and the prevention of more severe forms of the serotonin syndrome. Syndromes with scores of six and lower could be called serotonergic reactions, a term proposed by Fischer (1995).

A major shortcoming of this study is the naturalistic setting. The clinical decision to measure paroxetine plasma levels was the main inclusion criterion. Furthermore, a control group treated with a noradrenergic antidepressant would be important to clarify the specificity of the SSS for serotonergic side effects. Despite these shortcomings, this study gives first evidence that the Serotonin syndrome scale may become a useful extension of Sternbach's (1991) criteria for clinicians and scientists dealing with the serotonin syndrome. Furthermore, the scale may be helpful in extending focus on subacute and mild serotonergic reactions, which in our experience are not uncommon in patients treated with SSRI.

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