HYPONATREMIA AND THE SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE ASSOCIATED WITH THE USE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS: A REVIEW OF SPONTANEOUS REPORTS

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Abstract • Résumé

Objective: To review reported cases of hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with the use of selective serotonin reuptake inhibitors (SSRIs).

Data sources: A search of MEDLINE for reports of hyponatremia and SIADH associated with the use of fluoxetine, fluvoxamine, paroxetine or sertraline published between January 1980 and May 1995. Unpublished reports of cases were requested from the pharmaceutical industry, the Ontario Medical Association, the Health Protection Branch of Health Canada, the US Food and Drug Administration and the World Health Organization.

Data selection and extraction: Spontaneous reports from postmarketing surveillance.

Data synthesis: A total of 736 cases of hypernatremia and SIADH associated with SSRI use were reported. Fluoxetine was involved in 554 (75.3%) of the cases, paroxetine in 91 (12.4%), sertraline in 86 (11.7%) and fluvoxamine in 11 (1.5%). Reports of 30 cases were published. The remaining 706 cases were reported to monitoring bodies and the pharmaceutical industry. According to information in the published reports, the median time to onset of hyponatremia was 13 days (range 3 to 120 days). Most (83%) of the published cases involved patients 65 years of age or more, as compared with 74% of the unpublished cases.

Conclusion: Elderly people may be at increased risk for hyponatremia associated with SSRI use. Physicians caring for elderly patients should be aware of this potentially serious but reversible adverse effect. Further research is required to determine the incidence of this adverse effect, the relative risk of hyponatremia and SIADH in different age groups and the risk associated with different SSRI drugs.

Objectif : Examiner des cas signalés d'hyponatrémie et de syndrome d'antidiurèse inappropriée liés à l'utilisation d'inhibiteurs spécifiques du recaptage de la sérotonine.

Sources de données : Recherche dans MEDLINE de comptes rendus d'hyponatrémie et de syndrome d'antidiurèse inappropriée liés à l'utilisation de fluoxétine, de fluvoxamine, de paroxétine ou de sertraline, publiés entre janvier 1980 et mai 1995. On a demandé des comptes rendus de cas non publiés à l'industrie pharmaceutique, à l'Association médicale de l'Ontario, à la Direction générale de la protection de la santé de Santé Canada, à la Food and Drug Administration des États-Unis et à l'Organisation mondiale de la santé.

Sélection et extraction des données : Rapports spontanés issus des activités de pharmacovigilance.

Synthèse des données : On a signalé au total 736 cas d'hypernatrémie et de syndrome d'antidiurèse inappropriée liés à l'utilisation d'inhibiteurs spécifiques du recaptage de la sérotonine. La fluoxétine était impliquée dans 554 (75,3 %) des cas, la paroxétine dans 91 (12,4 %), la sertraline dans 86 (11,7 %), et la fluvoxamine dans 11 (1,5 %). Des comptes rendus ont été publiés sur 30 cas. Les 706 cas restants ont été signalés aux organismes de surveillance et à l'industrie pharmaceutique. Selon les renseignements

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r prescribing information see page 596

contenus dans les rapports publiés, la période moyenne d'apparition de l'hyponatrémie s'est établie à 13 jours (fourchette de 3 à 120 jours). La plupart (83 %) des cas publiés mettaient en cause des patients de 65 ans ou plus, comparativement à 74 % des cas non publiés.

Conclusion : Les personnes âgées peuvent risquer davantage d'être atteintes d'hyponatrémie liée à l'utilisation d'inhibiteurs spécifiques du recaptage de la sérotonine. Les médecins qui traitent des patients âgés devraient être conscients de cet effet indésirable qui pourrait être grave, mais qui est réversible. Des recherches plus poussées s'imposent pour déterminer l'incidence de cet effet indésirable, le risque relatif d'hyponatrémie et de syndrome d'antidiurèse inappropriée dans des groupes d'âge différents et le risque lié aux différents inhibiteurs spécifiques du recaptage de la sérotonine.

The use of selective serotonin reuptake inhibitors (SSRIs) in elderly people has been associated with reports of hyponatremia, some of which are compatible with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Internists and primary care physicians are most often responsible for managing elderly patients when they present with electrolyte disturbances, yet few physicians are aware of this potentially fatal but reversible adverse effect. Most published reports on this topic have appeared in the psychiatric literature.

Patients with hyponatremia may be asymptomatic or present with nausea, anorexia, muscle cramps, weakness, fatigue, confusion and disorientation. Severe hyponatremia may result in serious neurologic sequelae such as coma and seizures, and death. Both the magnitude and rate of development of hyponatremia are important determinants of the severity of clinical symptoms.[1]

SIADH, the syndrome of inappropriate secretion of antidiuretic hormone, occurs in association with reduced serum osmolality. This condition is characterized by hypotonic hyponatremia (serum sodium level of less than 130 mmol/L), inappropriately elevated urine osmolality (usually more than 200 mmol/kg) relative to plasma osmolality, an elevated urine sodium level (typically greater than 20 mmol/L), expanded extracellular volume, and normal renal, adrenal and thyroid function.[2] The syndrome may be caused by a number of disease processes (e.g., malignant neoplasms, nonmalignant pulmonary disease and central nervous system disorders) and medications. The list of medications known to cause SIADH includes several psychotropic agents. We believe that SSRI antidepressants should be added to that list.

We reviewed cases of SIADH and hyponatremia associated with SSRI use published in the literature as well as unpublished reports collected from postmarketing surveillance. We examined trends in these reports in order to identify the scope of the problem and possible risk factors for these underrecognized adverse effects.

Methods

We searched MEDLINE, using manual cross-referencing, for reports of SSRI use and SIADH or hyponatremia published between January 1980 and May 1995 using the following MeSH terms: "water-electrolyte imbalance," "hyponatremia," "inappropriate ADH syndrome" and "serotonin uptake inhibitors." In addition, we collected case reports from the manufacturers of the SSRIs currently available in North America. We sent requests for information to the adverse drug monitoring programs of the Ontario Medical Association (OMA), the Health Protection Branch (HPB) of Health Canada, the US Food and Drug Administration (FDA) and the World Health Organization (WHO). Duplicate reports were identified on the basis of demographic details and case descriptions. When overlap occurred, the reports were attributed to the highest ranking source according to the following hierarchy: published literature, WHO, HPB, OMA or FDA, and the Canadian pharmaceutical industry.

We did not attempt to assess causality or the criteria used to diagnose hyponatremia or SIADH in the reports received from independent monitoring bodies. In the published cases two of us (B.A.L. and S.R.K.) assessed causality by consensus using a validated 10-item rating system for adverse drug reactions.[3]

Published reports were analysed separately from unpublished ones for trends, because the information in the published reports was felt to be more detailed and more reliable.

Results

We found 736 cases of hyponatremia associated with SSRI use in the published literature and unpublished reports (Table 1). Reports from the FDA would have been provided at an estimated cost of US$1600 and therefore were not requested for inclusion in our review. However, most of the reports sent to the WHO originated from the United States (84% [507/605]) and therefore were likely part of the unreviewed FDA database.

Published reports

We found 30 cases in the literature (Table 2).[4–32] Twenty-five (83%) involved patients over 65 years of age (range 47 to 92 years). The median time to onset of hyponatremia was 13 days (range 3 to 120 days). In all

cases the patient's condition returned to normal 2 to 28 days after discontinuation of the SSRI; in one case the SSRI was not withdrawn and fluid restriction was temporarily required to normalize the serum sodium level.[5] The results of rechallenge were reported for five cases. An 83-year-old woman had recurrence of hyponatremia within 3 weeks after rechallenge with fluoxetine.[14] A 60-year-old man required ongoing fluid restriction to control his serum sodium level after rechallenge with sertraline.[20] Jackson and associates[15] described a 77-year-old woman in whom hyponatremia compatible with SIADH developed after treatment with fluoxetine; the electrolyte disturbance recurred within 4 days after switching to sertraline. Two other patients were rechallenged with the implicated SSRI and were able to tolerate the drug.[8,20]

Challenge with another SSRI from the same class was also reported. In the case involving the 83-year-old woman reported by Druckenbrod and Mulsant[14] SIADH developed 3 months after the start of fluoxetine therapy. Demeclocycline was required to control the hyponatremia. The patient later received a trial of sertraline, which was discontinued because of diarrhea. There was no mention of electrolyte disturbance, nor was the duration of the sertraline therapy indicated. In the case involving the 77-year-old woman described by Jackson and associates[15] the patient's sodium level returned to normal after withdrawal of the fluoxetine. When she was subsequently given sertraline, electrolyte disturbance compatible with SIADH recurred.

There was no association found between the SSRI dose or the patient's age and the time of onset of hyponatremia in any of the published cases. Neither of these two variables correlated with the severity of the hyponatremic response. The SSRI dose was within the suggested therapeutic dose range in all cases.

Concomitant illness or use of medications known to cause SIADH could be implicated in some of the cases.[6,10,13,16–18,20,21] Other reports ruled out the common causes of SIADH, such as pulmonary or cerebral pathology, and renal, thyroid or adrenal disease.[5,7–9,11,14,19,22] The positive temporal association, the lack of alternative causes and the reversal of hyponatremia after discontinuation of the SSRI offered good evidence of a causal relationship. Using the adverse drug reaction rating scale to assess causality we found that 18 (60%) of the 30 reports were possibly related to the SSRI, 9 (30%) were probably related and 3 (10%) were definitely related.

Table 1: Summary of reports of hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with the use of selective serotonin reuptake inhibitors (SSRIs)

Variable	No. (and %) of cases	
Country		
United States	523	(71.1)
Australia and New Zealand	50	(6.8)
United Kingdom	26	(3.5)
Canada	26	(3.5)
Europe	22	(3.0)
South Africa	1	(0.1)
Not specified	88	(12.0)
Source		
World Health Organization	605	(82.2)
Health Protection Branch (Health Canada) or Ontario Medical Association	10	(1.4)
Pharmaceutical industry	91	(12.4)
Published literature	30	(4.1)
Age, yr		
< 65	136	(18.5)
≥ 65	410	(55.7)
Not specified	190	(25.8)
Sex		
Male	144	(19.6)
Female	444	(60.3)
Not specified	148	(20.1)
SSRI		
Fluoxetine	554*	(75.3)
Fluvoxamine	11	(1.5)
Paroxetine	91*	(12.4)
Sertraline	86*	(11.7)
Total	736	(100.0)

*In two cases the patient was exposed to both fluoxetine and paroxetine, and in four the patient was exposed to both fluoxetine and sertraline.

Unpublished reports

There were 706 reports of hyponatremia associated with SSRI use submitted to the OMA, the HPB, WHO and the pharmaceutical industry (Table 3). In 516 cases the patient's age was reported: at least 384 (74.4%) of these involved patients over 65 years. According to information from 266 cases, the median time to onset of hyponatremia was 13 days (range 1 to 787 days). In almost all (95.8% [346/361]) of the cases in which the results of discontinuation of the drug were reported, the hyponatremia reversed after withdrawal of the SSRI. Challenge with the drug, attempted in 24 cases, resulted in recurrence of the hyponatremia in 16 cases (66.7%). Challenge with an alternative antidepressant from the same SSRI class was reported in two cases in which hyponatremia had developed in 83-year-old women while they were taking fluoxetine. One woman was subsequently treated with fluvoxamine, the other with paroxe-

Table 2: Details from published reports of hyponatremia and SIADH associated with SSRI use*

Reference	Age/ sex	Daily dose, mg	Lowest serum sodium level, mmol/L	Serum osmolality, mmol/kg	Urine osmolality, mmol/kg	Urine sodium level, mmol/L	No. of days to onset	No. of days to recovery after drug withdrawal	Other medications	Additional information
Fluoxetine										
Hwang et al[4]	75/M	20	126	264	417	NR	10	10	NR	Switched to trazodone, no further hyponatremia
Cohen et al[5]	82/F	40	125	265	NR	74	3	7	NR	R, TFT and Adr results normal
	79/F	20	129	NR	NR	46	42	5	NR	R, TFT and Adr results normal; positive rechallenge with fluoxetine
	84/F	40	124	264	NR	54	21	SSRI continued	NR	R, TFT and Adr results normal
	85/M	20	126	272	NR	84	7	14	NR	Thalamic infarct; R and TFT results normal; ACTH stimulation test results normal
Gommans et al[6]	75/F	20	116	242	337	91	12	6	Ranitidine	R and TFT results normal; cortisol level normal
Marik et al[7]	60/F	NR	106	225	452	50	120	14	Lorazepam	CXR, abdominal ultrasound, TFT and Adr results normal
Staab et al[8]	59/M	80	125	269	509	45	21	3	None	R, TFT and Adr results normal; no occult malignant disease; negative rechallenge with fluoxetine
Vishwanath et al[9]	53/F	20	122	258	385	102	14	2	NR	TFT result, CXR and CT of head normal
Blacksten et al[10]	92/F	20	98	214	465	114	13	8	Indapamide,‡ levothyroxine, alprazolam	R, TFT and Adr results normal; CXR and head CT normal
Kazal et al[11]	83/F	20	124	256	573	85	6	13	Trimethoprim–sulfamethoxazole, timolol, calcium	TFT and Adr results normal; CXR and head CT normal
Ball et al[12]	74/F	20	116	NR	NR	42	14	14	Thioridazine‡ (two doses only)	R, TFT and liver function results normal; CXR and head CT normal; MRI scan of head showed multiple white-matter lesions
Pillans et al[13]	76/F	20	116	242	337	91	13	22	Ranitidine, paracetamol–dextropropoxyphene, furosemide‡	R results normal
	81/F	20	128	NR	NR	NR	8	4	Cyclopenthiazide,‡ captopril, chlormethiazole‡	R and TFT results normal
	76/F	20	120	NR	NR	NR	19	NR	Nifedipine	
	88/F	20	121	253	456	NR	15	NR	Prednisone, salbutamol, verapamil,	No improvement after withdrawal of diuretic

									hydrochloro-thiazide/amiloride‡	
	68/F	20	120	NR	NR	NR	60	NR	NR	
	87/F	20	114	NR	NR	NR	42	NR	Paracetamol	R results normal
	84/F	20	117	NR	NR	NR	13	NR	Allopurinol	R results normal
Druckenbrod et al[14]	83/F	40	109	242	530	46	120	28	Calcium carbonate, ferrous sulfate, vitamins	TFT and Adr results normal; CXR and MRI scan of head normal; demeclocycline required to control hyponatremia; positive rechallenge with fluoxetine
Jackson et al[15]†	77/F	20	104	216	334	NR	12	NR	None	R results normal; hyponatremia recurred after switch to sertraline
Fluvoxamine										
McHardy[16]	70/F	100	114	239	392	NR	5	3	Co-amoxiclav, oxprenolol, bendrofluazide,‡ triazolam, potassium	R, Adr and liver function results normal; CXR normal; no improvement after discontinuation of co-amoxiclav, bendrofluazide and triazolam
Paroxetine										
Goddard et al[17]	69/F	40	126	NR	NR	NR	16	2	Acetylsalicylic acid, lactulose	Head CT showed multiple infarcts
Chua et al[18]	78/F	NR	115	256	369	NR	5	10	Lisinopril	R results normal; CXR normal
	76/M	NR	112	246	292	NR	7	4	Nitrazepam (overdose)	CXR showed signs of pneumonia
Sertraline										
Jackson et al[15]†	77/F	50	126	246	518	NR	4	3	NR	Previous reaction when treated with fluoxetine
Crews et al[19]	73/M	50	118	251	511	33	5	NR	Diazepam, quinine, ranitidine, nifedipine	R, TFT and Adr results normal; head CT normal; previous use of nortriptyline and amitriptyline resulted in hyponatremia
Doshi et al[20]	47/M	100	118	237	229	38	120	14	Carbamazepine‡	R, TFT and Adr results normal; no evidence of malignant disease; negative rechallenge with sertraline
Llorente et al[21]	92/M	50	122	260	361	59	7	7	Doxepin‡	R, Adr and TFT results normal; presented after overdose of sertraline (350 mg)
Thornton et al[22]	60/M	50	126	256	389	NR	5	NR	NR	TFT and Adr results normal; head CT normal; positive rechallenge with sertraline, serum sodium level controlled with fluid restriction
	72/F	75	105	217	393	NR	4	NR	NR	TFT and Adr results normal; head CT normal

*R = renal test, TFT = thyroid function test, Adr = adrenal function test, ACTH = adrenocorticotropin, CXR =chest x-ray, CT = computed tomogram, MRI = magnetic resonance imaging, NR = no report, NA = not available.
†Single case appears twice in this table, as separate entries under fluoxetine and sertraline.
‡Medications associated with SIADH.

tine. Neither subject experienced any further electrolyte disturbance.

In at least 390 cases patients were receiving drugs other than the SSRI. Exposure to other agents known to be associated with hyponatremia or SIADH occurred in 193 cases. The most commonly implicated drugs were diuretics (30.0% of cases in which concomitant drug use was reported), neuroleptics (15.1%), narcotics (6.7%) and oral hypoglycemic agents (4.1%). In addition, 19 patients (4.9%) were using a corticosteroid preparation, and 33 (8.5%) were receiving thyroid hormone therapy. Despite the use of medications that may have contributed to hyponatremia, in 112 (58.0%) of the 193 cases the serum sodium levels returned to normal after withdrawal of the SSRI; hyponatremia persisted in only 3 cases (1.6%), and in the remainder the results of discontinuation of the SSRI were not reported. Additional information regarding investigations to rule out other medical causes of hyponatremia and SIADH was not available. Causality was assessed by a drug-monitoring body in only 72 (10.2%) of cases; 40% of these cases were rated as probably related and 54% as possibly related to SSRI use.

Discussion

There were 30 documented cases of hyponatremia associated with SSRI used in the literature. In addition, over 700 cases of varying clinical detail were reported to the pharmaceutical companies and independent drug-monitoring agencies. With the estimated number of patients exposed to an SSRI exceeding 10 million worldwide, hyponatremia is still considered a rare adverse effect. Postmarketing surveillance cannot be used to estimate the incidence of an adverse drug effect. Nor can we determine whether one SSRI is more likely than another in the same class to cause hyponatremia. However, we found that for each SSRI the proportion of spontaneous reports of adverse reactions received by the WHO documenting hyponatremia or SIADH was similar (fluoxetine 0.96%, fluvoxamine 0.54%, sertraline 1.26% and paroxetine 1.33%). Although most of the cases in our review involved fluoxetine, this may reflect higher utilization of this SSRI rather than an increased risk of hyponatremia.

It has been suggested that SSRI-induced SIADH may be a phenomenon unique to elderly patients.[11] Although

Table 3: Details from unpublished reports of hyponatremia and SIADH associated with SSRI use

Variable	Drug; no. of cases*				
	All reports	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Sex					
Male	136	101	3	16	18
Female	422	321	5	61	38
Not specified	148	111	2	11	24
Age					
< 65 yr	132	103	1	20	10
≥ 65 yr	384	285	7	54	41
Not specified	190	145	2	14	29
Mean age (and standard deviation), yr	70 (14)	70 (14)	77 (12)	72 (16)	71 (14)
Age range, yr	6–94	6–94	53–88	21–92	24–90
Mean daily dose (and range), mg		24.5 (12.5)	62.5 (23.1)	17.0 (5.4)	64.4 (34.8)
Dose range, mg		5–80	50–100	10–30	50–200
Median time to onset (and range), d	13 (0–787)	14 (0–787)	14 (2–61)	10 (0–739)	10 (0–222)
Drug challenge					
Symptoms recurred	16	13	0	2	3
Symptoms did not recur	8	6	0	1	1
Unknown reaction	682	514	10	85	76
Drug discontinued					
Symptoms resolved	346	250	6	56	39
Symptoms did not resolve	15	8	0	5	2
Results unknown	344	274	4	27	39
Drug not discontinued	1	1	0	0	0
Total no. of reports	706†	533†	10	88†	80†

*Unless stated otherwise.
†In two cases the patient was exposed to both fluoxetine and paroxetine, and in three the patient was exposed to both fluoxetine and sertraline.

The patients featured in the reports we reviewed ranged in age from 6 to 94 years, most were elderly. A number of physiologic changes in water homeostasis may predispose elderly people to hyponatremia from any cause. In this age group, the maximal diluting and concentrating capacity of the kidney is impaired,[11,23] and ADH secretion may be slightly increased.[24] In addition, the ADH response to osmolar stimuli has been shown to be greater in elderly people than in young control subjects.[25] This increased osmosensitivity may increase the risk for SIADH in elderly people. Alternatively, hyponatremia may simply not be tolerated as well in elderly patients and thus be more likely to require medical attention.

Sixty percent of the cases we reviewed involved females and 20% males; in the remaining 20% sex was not specified. In general, adverse drug reactions are reported to occur more frequently in female patients.[26–28] Several factors may contribute to an apparent sex-related difference in the occurrence of hyponatremia and SSRI use. Female patients may have increased exposure to SSRIs because the incidence of depression is increased in the female population,[29] or there may be sex-related bias in prescribing patterns. Patterns of health care utilization have been shown to differ between male and female patient populations.[30,31] This may affect not only drug exposures but also the detection, documentation and reporting of adverse reactions.

Hyponatremia associated with SSRI use usually develops soon after the start of drug therapy. The median time to onset in the cases we reviewed was 13 days (based on reports from published and unpublished sources). Three quarters of the cases presented within 30 days after the start of therapy. Routine monitoring of electrolyte levels in elderly patients may be worth while, especially during the first 2 to 4 weeks of treatment. However, hyponatremia may occur late in the course of SSRI therapy. In our series, 29% of the patients presented more than 3 months after SSRI therapy had been started.

Our assessment of causality in the published cases resulted in 40% being rated as either definitely or probably related to SSRI use and the remaining cases being rated as possibly related. Although we did not attempt to assess causality in the unpublished cases, we found that reversal of hyponatremia after withdrawal of the SSRI occurred in 58% of the 193 cases in which there was concomitant use of pharmaceutical agents known to cause SIADH. Challenge with the implicated SSRI, attempted in 27 cases, resulted in the recurrence of hyponatremia in 18. Some cases of drug-induced SIADH have been reported to be transient.[32] This may explain the lack of response to the challenge seen in the other nine cases.

Hyponatremia is likely an effect common to this class of antidepressants. Considering the structural heterogeneity of the four SSRIs reviewed, the adverse effect is unlikely to be related to chemical structure. There are three possible ways drugs can affect water homeostasis: they can increase ADH secretion centrally, potentiate the effect of endogenous ADH at the renal medulla, and reset the osmostat, thus lowering the threshold for ADH secretion.

ADH secretion from the posterior lobe of the pituitary gland is thought to be affected by such nonosmolar factors as angiotensin II, noradrenaline, acetylcholine and endorphin levels.[33,34] Dopamine antagonists such as haloperidol and domperidone have been shown in animal models to facilitate ADH secretion[35–37] and increase thirst by increasing angiotensin II levels.[38] Noradrenaline induces the release of ADH via α_1-adrenergic receptors; stimulation of α_2-adrenergic and ß-adrenergic receptors may, however, inhibit ADH release.[39,40] Serotonin-mediated effects on 5-HT_2 and 5-HT_{1C} receptors have been shown to induce release of ADH.[41,42] Although the SSRIs are believed to be highly selective in their effect on serotonin reuptake, animal studies have shown that the SSRIs have some inhibitory effects on the reuptake of dopamine and noradrenaline. However, the potency of these effects varies greatly between the different SSRIs.[43,44] The effect of various psychotropic drugs on neurotransmitters has been speculated to contribute to excess ADH secretion; however, the exact mechanism of SSRI-induced SIADH remains unknown.

Hyponatremia associated with SSRI use may be a manifestation of a drug interaction. SSRIs are known to inhibit a number of cytochrome P450 isoenzymes.[45] In several of the cases we reviewed, the patients were concurrently receiving a drug known to cause SIADH. By inhibiting the metabolism of concomitant drugs such as neuroleptics, adverse effects on sodium metabolism may be augmented.

There are several limitations one must consider when evaluating reports from postmarketing surveillance. An incidence rate cannot be estimated, because the number of patients exposed is not available. Voluntary reporting may underrepresent the true incidence of adverse drug reactions. Reports may be biased because of perceived severity of the adverse effect, media bias or physician awareness of a possible drug association. In addition, the quality of reports can vary greatly. In some reports, even the most basic demographic information such as age and sex were missing. Moreover, there may be overlap of reports between the various sources. We identified 25 cases that had been reported to more than one source. Duplication of reports may result in an overestimation of the event, an especially important problem for rare adverse events.

The problem we encountered in attempting to access information from the FDA has been reported previously.[46] Willingness of drug-monitoring bodies to share information for medical practice and research in a timely

fashion and without exorbitant service charges should be ensured. In order for information regarding adverse drug reactions to be applied, accessibility, analysis and dissemination of information are critical.

Conclusion

There is a large number of reports of SIADH and hyponatremia associated with SSRI use. This form of hyponatremia usually develops soon after the start of SSRI therapy, and the electrolyte disturbance in almost all cases reverses after withdrawal of the drug. There is no apparent relation with dose. Advanced age appears to be a risk factor for this adverse effect, as does the concomitant use of diuretics. Increased physician awareness of this potentially serious but treatable adverse effect is needed. The use of SSRI antidepressants should be included in the differential diagnosis of drug-induced hyponatremia. Clinical deterioration should prompt an evaluation of electrolyte levels. Elderly patients should be monitored closely in the first 4 weeks of SSRI therapy for clinical signs suggestive of hyponatremia. Further research is required to evaluate the relation between age, sex and the risk of SSRI-induced hyponatremia. In addition, the relative risk of hyponatremia associated with each SSRI drug needs to be determined.

Since this review was completed, six additional cases of hyponatremia and SIADH associated with SSRI use have appeared in the literature.[47–50] Five of the patients were women, and five were over 65 years of age.

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