# THE ELDERLY,

# ARGININE VASOPRESSIN

# &

# SELECTIVE SEROTONIN REUPTAKE INHIBITORS

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# CONTENTS

## Discussion

## ABSTRACT

The association between selective serotonin reuptake inhibitors (SSRIs) and hyponatraemia has been well documented, the elderly appearing to be at greatest risk. An analysis of data of hyponatraemia in the elderly using SSRIs from all published cases and from the Committee on Safety of Medicines found that the mean time to detection was about 3 weeks after commencing SSRIs. A wide range of time to detection (1-253 days) and non-specific symptoms suggest hyponatraemia is detected by chance rather than being specifically looked for. This is probably a sporadic, idiosyncratic phenomenon that is not dose related as AVP function determined by serum and urine concentrations was found to be normal in six elderly patients using sertraline. In the elderly there are physiological changes, a high prevalence of medical illnesses and concomitant drug use which may precipitate hyponatraemia. Together with a risk of altered water regulation in psychiatric illness this may account for the particular susceptibility of this group to hyponatraemia whilst using SSRIs.

## AIMS & HYPOTHESIS

This dissertation will explore the physiology of Arginine Vasopressin and how changes in this system along with other physiological changes in the elderly make the elderly susceptible to hyponatraemia. This problem will then be explored in the context of elderly people with depression using SSRIs which are known to cause hyponatraemia.

In the first part of the research section the aims are to report the published cases of hyponatraemia occurring whilst using SSRIs from the United Kingdom and specifically focus on cases in people 60 years and older. Secondly to re-analyse all case reports in the literature looking only at this population. The third aim was to investigate whether dysregulation of vasopressin function in the elderly using SSRIs is a sporadic or usual phenomenon.

The null hypothesis is that AVP function is not disturbed by SSRIs.

# INTRODUCTION

## 1.0 General

The elderly are a unique group and require special consideration when managing their mental health. On a psychological level they are confronting issues surrounding their independence, physical health and mortality so added mental illness can be devastating and frequently results in loss of independence, deterioration in physical health and even death. Dementia and depression are two mental illnesses that occur more frequently in this population and require treatment with psychoactive drugs. Insomnia is also often treated with psychoactive drugs. Part of the normal aging process involves a loss of

physiological functional reserve. This means any minor disturbances by illness or drugs can alter physiological function significantly. The elderly are more likely to have degenerative illnesses, particularly of the cardiovascular system, and are more likely to be taking medication, both prescribed and over the counter preparations. Polypharmacy is common.

It is thus important to establish what physiological changes may be precipitated by a certain mental illness and how this occurs. Models involving cortisol and depression are well evolved. Psychoactive drugs may also affect physiological function themselves. This is superimposed on the physiological changes that have occurred due to aging, any underlying medical condition or other medication. These factors may interact with each other or have individual effects.

New psychoactive drugs are being developed and promise fewer side effects reducing the risk of adverse reactions in the elderly. However, the effects of these drugs on physiological function need to be researched as it may give greater understanding to the pathophysiology of the mental illness and the mechanism of action of the drug. This will also make it easier to administer these drugs more safely because possible physiological complications can be screened for.

Selective serotonin reuptake inhibitors (SSRIs) were introduced as safe antidepressant alternatives to tricyclic antidepressants and monoamine oxidase inhibitors and they have proved to be thus making them suitable for use in the elderly. Hyponatraemia associated with SSRI use is a well documented adverse reaction and may result in serious morbidity

or mortality. Exploring the frequency, characteristics and mechanism of this hyponatraemia will identify the extent of the problem, which people are at risk and allow safer use of these drugs. It will also allow some unraveling of the complex physiological interactions that occur in the elderly. Finally it may shed some more light on physiological changes associated with depression, particularly changes in arginine vasopressin (AVP) function.

### 1.1 Depression in the elderly

Depression is a serious illness that is common in the elderly. Depressive symptoms occur in around 15% of people 65 years and older with 3-10% fulfilling criteria for major depressive disorder (Alexopoulos, 1996, Reynolds, 1996, Rothschild, 1996, Skerritt *et al.*, 1997). In medically ill elderly patients the incidence of major depression has been reported as high as 31% and 45% of hospitalised elderly (Newhouse, 1996). Suicide rates rise dramatically in old age. The 1986 USA reported suicide rates were 21.6 per 100 000 for persons 65 years or older compared with 12.8 per 100 000 for the general population. For elderly white men this rate was 40–75 per 100 000 (Newhouse, 1996, Reynolds 1996). Untreated depression in the elderly is associated with considerable morbidity and mortality and may increase healthcare costs. The 1991 National Institute of Health consensus development panel identified five objectives of treatment of depression in the elderly. These were 1) to reduce depressive symptoms, 2) to improve quality of life, 3) to

reduce the risk of relapse and recurrence, 4) to improve medical health, 5) to reduce healthcare costs and mortality (Reynolds, 1996).

The effective treatment of depression in the elderly is complicated by comorbid physical illnesses, compliance difficulties and age related changes in drug absorption, distribution and metabolism (Newhouse, 1996, Skerritt *et al.*, 1997). Changes in body weight and ratio of adipose tissue to lean body mass affect drug distribution and reduced renal and hepatic function influence drug clearance and plasma levels. Erratic failure of different enzyme systems also helps explain individual variation in drug metabolism (Skerritt *et al.*, 1997). The elderly are more sensitive to the adverse effects of pharmacotherapy for depression and they are more likely to be on several other drugs increasing the risk of interactions (Rothschild, 1996). The adverse effects of drugs is one of the five most important quality of care problems in older people and adverse drug effects are most consistently linked to polypharmacy (Hanlon *et al.*, 1997). In one report 35% of older ambulatory patients using 5 or more medications experienced an adverse drug reaction over a one-year period. Of these 10–11% had to attend a hospital emergency room or receive inpatient treatment (Hanlon *et al.*, 1997). Psychotropic drugs, including all antidepressants, are among the most common classes of drugs associated with adverse drug effects in the elderly. High rates of psychotropic drug use have been described in the elderly with falls, impaired cognition and impaired self-care abilities being adverse outcomes associated with these drugs. In a report on 10263 elderly patients the frequencey of falls was 120% greater in users of antidepressants than non users (Ebly *et al.*, 1997).

## 2.0 Selective serotonin re-uptake inhibitors in the elderly.

SSRIs were a novel group of antidepressants introduced with fluoxetine in the 1970s. Several others have appeared on the market since and the commonly used ones are fluoxetine, paroxetine, fluvoxamine, citalopram and sertraline. (Grebb, 1995). The half lives of SSRIs range from 2-3 days for fluoxetine and 7-15 days for its active metabolite, norfluoxetine, to about 7-33 hours for the rest (Grebb, 1995, Preskorn, 1997, Skerritt *et al.*, 1997). They are all well absorbed after oral ingestion. They undergo extensive oxidative metabolism mediated by different cytochrome P450 isoenzymes in the liver (Preskorn, 1997). They all have specific activity inhibiting neuronal serotonin re-uptake without significant effects on norepinephrine or dopamine re-uptake (Grebb, 1995, Preskorn 1997). They all have similar clinical efficacy in depression. Some of them have been shown to be effective in other conditions e.g. obsessive compulsive disorder, bulimia, anxiety, panic disorder (Grebb, 1995).

SSRIs have different side effect profiles to tricyclic, heterocyclic and monoamine oxidase inhibiting antidepressants because they have little effect at dopaminergic, $\alpha$1-adrenergic, histaminergic and cholinergic receptors (Newhouse, 1996). They therefore lack the significant anticholinergic, cardiovascular and sedative effects of tricyclic antidepressants. SSRIs represent an important advance over tricyclic antidepressants with respect to cardiac effects. SSRIs have a much smaller conduction effect in the heart and do not produce clinically significant ECG changes. They are safer in patients with pre-existing cardiac disease and undetected cardiac disease. They are also relatively safe in

overdose (Reynolds, 1996, Skerritt *et al.*, 1997). SSRIs do not interfere with cognitive function, which is commonly a problem with psychotropic medication in the elderly (Rothschild, 1996, Ebly *et al.*, 1997, Skerritt *et al.*, 1997). They are also less associated with falls than tricyclic antidepressants (Grebb, 1995).

The most common adverse effects associated with SSRIs are gastrointestinal disturbances especially nausea, headaches, insomnia, somnolence, agitation, sexual dysfunction and loss of weight (Reynolds, 1996, Rothschild, 1996, Skerritt *et al.*, 1997). The frequency of adverse effects of SSRIs are probably similar to tricyclic antidepressants, but these effects are less troublesome and are associated with reduced adverse effect burden. Patients on SSRIs are less likely to stop their medication because of adverse drug effects that those on tricyclic antidepressants (Newhouse, 1996, Skerritt *et al.*, 1997).

Results of controlled studies suggest SSRIs are efficacious in the treatment of depression in the elderly and although few trials have been done comparing tricyclic antidepressants and SSRIs, those that have been done generally show equal efficacy (Newhouse, 1996, Rothschild, 1996, Skerritt *et al.*, 1997). There have been reports suggesting fluoxetine has low efficacy in the elderly with unipolar depression and older cardiac patients with severe melancholic depression, but more information is needed to confirm such findings (Reynolds, 1996). The reports of SSRIs in the elderly are difficult to interpret because sample sizes tend to be small, definitions of elderly differ and attrition rates tend to be high (Skerritt *et al.*, 1997)

## 2.1 Cytochrome P450 enzymes, SSRIs and drug interactions.

There are more than 30 related enzymes in the family of cytochrome P450 enzymes. They are largely located in the endoplasmic reticulum of hepatocytes, but also occur in other sites e.g. intestinal mucosa. They are involved in oxidative metabolism of several endogenous substances e.g. prostaglandins, fatty acids, steroids, and also a number of drugs. The majority of antidepressants and antipsychotics are metabolised by, or inhibit to a varying degree, one or more cytochrome P450 isoenzymes (Nemerof *et al.* 1996). The SSRIs in particular have been found to be potent inhibitors of several different isoenzymes thus affecting the metabolism of drugs that are substrates of these enzymes (Ereshefsky *et al.*, 1996, Nemerof *et al.*, 1996, Preskorn, 1997, Taylor & Lader, 1996). The size of this effect is illustrated in reports of tricyclic antidepressants plasma concentrations over baseline ranging 58-150% when co-administered with 50mg sertraline and 110-375% when co-administered with 20mg fluoxetine (Nemerof *et al.*, 1996). A drug can inhibit the activity of an isoenzyme without itself being a substrate at that site, so knowledge of the metabolic pathway of an SSRI does not predict its potential for drug interaction. Fortunately most drugs have several potential metabolic pathways and if a particular enzyme is inhibited its metabolism will continue albeit less efficiently (Ereshefsky *et al.*, 1996).

The roles of five cytochrome P450 isoenzymes have been established with respect to SSRIs and these are CYP 2D6, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 3A3/4 (Ereshefsky *et al.*, 1996, Nemerof *et al.*, 1996, Preskorn, 1997, Taylor & Lader, 1996).

Table 1 shows some substrates of these isoenzymes, table 2 shows the different inhibitory qualities of the different SSRIs and table 3 shows some other drugs that also inhibit some of these isoenzymes.

Some isoenzymes demonstrate genetic polymorphic distribution e.g. 4-10% Caucasians and 5-10% Mexican Americans are poor metabolisers at the CYP 2D6 site and 3-5% Caucasians, 18-23% African Americans and 8% Africans are poor metabolisers at the CYP 2C19 site. These groups of people would be at increased risk of adverse effects if they use drugs requiring metabolism by these isoenzymes (Ereshefsky *et al.*, 1996, Nemerof *et al.*, 1996). This would apply to paroxetine, sertraline, citalopram and fluoxetine.

Drugs with narrow therapeutic windows e.g. tricyclic antidepressants, theophylline, phenytoin, tolbutamide, carbamazepine, terfenadine, astemizole, type 1C antiarrhythmics and antipsychotics should be administered with caution in the presence of SSRIs. Genetic polymorphism hinders the prediction of clinically significant interactions (Nemerof *et al.*, 1996). SSRIs also have widely differing drug interaction potentials across the CYP isoenzyme systems (Ereshefsky *et al.*, 1996).

Enzyme inhibition is not the only mechanism whereby SSRIs interact with other drugs. SSRIs are highly protein bound, ranging from 80% for fluvoxamine to 99% for sertraline, so if administered with other highly protein bound drugs e.g. warfarin, digoxin, the

effects of these drugs are likely to be enhanced and require dose adjustment (Newhouse, 1996, Preskorn, 1997).

There are also drug interactions where the underlying mechanism is unclear e.g. 'serotonin syndrome' reported following use of a SSRI in conjunction with a monoamine oxidase inhibitor (Skerritt *et al.*, 1997).

These interactions are important in the elderly because they are more likely to have another illness requiring medication and they are the population in which polypharmacy is a problem.

| CYP 2D6 | CYP 3A3/4 | CYP 1A2 | CYP 2C9 | CYP 2C19 |
|---|---|---|---|---|
| Fluoxetine | Sertraline | Amitriptyline | Warfarin | Imipramine |
| Paroxetine | Amitriptyline | Clomipramine | Phenytoin | Clomipramine |
| Sertraline | Clomipramine | Imipramine | Tolbutamide | Citalopram |
| Venlafaxine | Imipramine | Caffeine | Diclofenac | Diazepam |
| Amitriptyline | Alprazolam | Clozapine | Mefenamic acid | Omeprazole |
| Clomipramine | Triazolam | Theophylline | Piroxicam | Propranalol |
| Desipramine | Midazolam | Propranalol | Naproxen | Hexobarbital |
| Nortryptiline | Diazepam | Paracetamol | Ibuprofen | Mephenytoin |
| Clozapine | Clozapine | Warfarin | | |
| Risperidone | Terfenadine | | | |
| Thioridazine | Astemizole | | | |
| Perphenazine | Loratadine | | | |
| Propranalol | Cisapride | | | |
| Metoprolol | Omeprazole | | | |
| Timolol | Diltiazem | | | |
| Encainide | Verapmil | | | |
| Flecainide | Nifedipine | | | |
| Propafenone | Carbamazepine | | | |
| Codeine | Erythromycin | | | |
| | Cyclosporine | | | |
| | Lidocaine | | | |
| | Cocaine | | | |
| | Quinidine | | | |
| | Tamoxifen | | | |
| | Cortisol | | | |
| | Testosterone | | | |
| | Oestradiol | | | |
| | Progesterone | | | |
| | Paracetamol | | | |

**Table 1. Some substrates of CYP isoenzymes.**

| Inhibition potency | CYP 2D6 | CYP 3A3/4 | CYP 1A2 | CYP 2C9 | CYP 2C19 |
|---|---|---|---|---|---|
| High | Fluoxetine<br>Paroxetine | Fluvoxamine | Fluvoxamine | Fluoxetine<br>Fluvoxamine | Fluvoxamine |
| Moderate to low | Sertraline<br>Citalopram | Fluoxetine | | | Fluoxetine |
| Low to minimal | Fluvoxamine | Sertraline<br>Paroxetine<br>Citalopram | Fluoxetine<br>Paroxetine<br>Sertraline<br>Citalopram | | |
| Unknown | | | | Paroxetine<br>Sertraline<br>Citalopram | Paroxetine<br>Sertraline<br>Citalopram |

**Table 2. Cytochrome P450 inhibition by different SSRIs including potency.**

| CYP 2D6 | CYP 3A3/4 |
|---|---|
| Quinidine | Ketaconazole |
| Fluphenazine | Erythromycin |
| Haloperidol | Nefazodone |
| Thioridazine | |
| Amitriptyline | |
| Desipramine | |
| Clomipramine | |

**Table 3. Other drugs that inhibit Cytochrome p450 isoenzymes.**

## 3.0 The physiology of Arginine Vasopressin

Arginine Vasopressin (AVP, also known as antidiuretic hormone) is synthesised as a portion of a large precursor protein from which AVP and Oxytocin are cleaved (Rinaman *et al.*, 1995). It is comprised of 9 amino acids as follows (Jackson, 1996):

Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly(NH2)

A number of vasopressin-like substances occur naturally, they are all nonapeptides (Jackson, 1996). AVP is synthesised in the perikarya of magnocellular neurons, which occur in four major clusters in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalalmus as well as in smaller groups in the accessory nuclei of the anterior hypothalamus. Long axons of these neurons take a loop-like pathway through the lateral retrochiasmic area, entering the median eminence and then run in the internal layer of this structure to terminate in the neurohypophysis. These neurons respond to osmotic stimuli (Antoni, 1993, Aguilera, 1994, Rinaman *et al.*, 1995, Jackson, 1996). The process of axonal transport of vasopressin-containing granules is rapid taking about 30 minutes from stimulus to newly synthesised hormone arriving at the posterior lobe (Jackson 1996). AVP is released from the neurohypophysis into the peripheral circulation.

AVP is also synthesised in neurons, mostly in the caudal PVN, that have central axonal projections. These are the 'parvicellular' neurons. An important group are the corticotrophin release hormone (CRH) neurons that also synthesise and secrete AVP. These neurons terminate in the median eminence secreting AVP into the pituitary portal system. Other centrally projecting AVP neurons have their perikarya in the stria terminalis, dorsomedial suprachiasmic nucleus, septal area, medial amygdala and locus coeruleus. The limbic structures, such as the lateral septum and amygdala, are particularly heavily innervated with AVP fibres. In the rat specific areas of innervation have been identified and they include the subparaventricular zone, dorsomedial nucleus of hypothalamus, medial and lateral preoptic areas, midline thalamic nuclei, habenular

nucleus, lateral septum, medial amygdala, periaqueductal grey area and ventral hippocampus. There are thus two different populations of AVP secreting neurons, the 'magnocellular system' projecting to the posterior pituitary and the 'parvicellular system' projecting to central brain areas. These two systems may have common and separate stimuli for AVP release. The afferent innervation of the PVN is very complex and it is not clear whether there is separate innervation of magnocellular and parvicellular neurons (Rinaman *et al.*, 1995).

In healthy adults the principal stimulus for AVP secretion is increased plasma osmolality. Severe hypovolaemia and hypotension are also powerful stimuli. Pain, nausea, hypoxia, and several endogenous hormones modify AVP secretion (Jackson, 1996). With osmolar stimulation, the threshold for secretion is approximately 280 mOsm/kg. Above this AVP levels rise in a steep linear fashion (Johnson *et al.*, 1994, Jackson, 1996). Osmolality above 290 mOsm/kg leads to an intense thirst sensation (Jackson, 1996). The magnocellular neurons in the SON and PVN of the hypothalamus respond directly to changes in osmolality, but also have afferent inputs from the subfornix and lamina terminalis (Jackson, 1996).

AVP release is also stimulated by reductions in blood volume and arterial blood pressure. AVP at high concentrations (40 times that required for antidiuresis) is a potent vasoconstrictor preventing haemodynamic collapse in conditions of hypovolaemia or hypotension (Rinaman *et al.*, 1995). The neuronal pathways involved are completely different to those involved with the osmoreceptors. Baroreceptors located in the left

atrium, left ventricle, and pulmonary veins sense blood volume. Baroreceptors in the carotid sinus and aorta sense arterial blood pressure. Information is relayed to the supraoptic nucleus via the vagus nerve, glossopharangeal nerve, solitary tract and caudal ventrolateral medulla. The relationship between blood volume / pressure and AVP release is exponential. This does not disrupt osmotic regulation, but resets the threshold for AVP secretion and alters the slope of the osmolality vs. AVP level relationship (Johnson *et al.*, 1994, Jackson, 1996).

AVP also has a role in the regulation of blood flow to the choroid plexus and the rate of cerebrospinal fluid (CSF) production. Normally AVP is found in the CSF at slightly higher concentrations than in plasma, this differential concentration being sustained by the blood brain barrier. AVP released into brain extracellular fluid diffuses into the CSF and there may also be direct secretion into the CSF in the third ventricle (Rinaman *et al.*, 1995).

Hormonal and neurotransmitter regulation of AVP secretion is complex and has not been fully elucidated. The literature is often contradictory (Jackson, 1996). Agents that seem to stimulate AVP secretion include acetylcholine, histamine, dopamine, glutamine, aspartate, cholecystokinin, neuropeptideY, substance P, vasoactive intestinal polypeptide, prostaglandins and angiotensin II. Substances that inhibit AVP secretion include atrial natriuretic hormone, gamma-aminobutyric acid and opioids (Jackson, 1996). In the CNS AVP acts as a neurotransmitter and neuromodulator participating in acquisition of some learned behaviour and acquisition of some complex social processes and in the

pathogenesis of specific psychiatric diseases. The exact role of AVP remains controversial (Jackson, 1996).

### 3.1 AVP, learning and behaviour.

In rats genetically deficient in AVP (Brattleboro rats) or made deficient by central administration of an AVP antiserum there is inferior performance in learning tasks. Experiments evaluating memory by administering AVP and oxytocin peripherally led to assumptions that oxytocin is 'amnestic' and AVP is 'memory enhancing'. These findings are difficult to interpret because any memory effects may have been related to the aversive visceral arousal induced by AVP. Furthermore only 0.002% of subcutaneously administered AVP reaches the CSF and concentrations in the limbic brain are unaffected. The two suggested effects potentiated by AVP in rats are social recognition and learned behaviour (Dantzer & Bluthe, 1993, Engelmann *et al.*, 1996). Centrally administered AVP to the septal area of rats has been shown to improve social recognition in males but it impairs their navigation in a maze, both processes involving memory. AVP administered in the septal area appears to be involved differentially in different behaviour tests. Intracerebrally administered AVP and oxytocin are involved in behavioural performance that is cued by olfactory signals and it appears to be related causally to reproduction. Predominantly sexual steroid-dependent vasopressinergic neurons are involved in these behavioural paradigms. The situation is further complicated by AVP acting on AVP receptors of non-neuronal structures e.g. glial cell or cerebral

microvessels, thus indirectly influencing interneuronal communication. Central release of AVP and oxytocin is paralleled by peripheral release, which in turn may induce metabolic and autonomic alterations that may support the effects triggered by the central peptides. These synergisms at different levels suggest the peptides themselves may provide the link between arousal, attention, emotion, learning, memory and behavioural performance, thus ensuring the relevant information is acquired and behavioural strategies established, stored and reactivated. The acquisition and early processing of information seems more sensitive to AVP and Oxytocin than the storage and recall and these peptides are predominantly involved in the emotional evaluation of incoming information (Engelmann *et al.*, 1996).

**3.2 Stress and AVP secretion.**

The normal physiological response to acute stress is activation of the hypothalamic-adrenal-pituitary axis resulting in elevated circulating glucocorticoids and glucocorticoid negative feedback to the hypothalamus and pituitary. Among the PVN parvicellular nuclei there are two populations of cortico-trophic hormone (CRH) neurons. One expresses pro-AVP peptides and the other does not. These populations are topographically separate and are possibly under separate control. The former is a probable source of portal AVP as AVP and CRH occupy the same secretory granules (Antoni, 1993, Aguilera 1994). AVP and CRH are released from the median eminence into the pituitary portal blood system and carried to the anterior lobe of the pituitary

gland stimulating adreno-corticotrophic hormone (ACTH). AVP binds V1b receptors and potentiates CRH-induced ACTH secretion. ACTH stimulates release of glucocorticoid from the adrenal glands (Rinaman *et al.*, 1995, Aguilera, 1994). It has been hypothesised that AVP is the dynamic component in the AVP/CRH combination that stimulates ACTH release because AVP receptor and secretion changes, rather than CRH receptor and secretion changes, parallel the changes in ACTH responsiveness. CRH may give a trophic or permissive signal allowing the action of AVP. During chronic stress the ACTH response is altered and this is determined by the AVP:CRH secretion ratio. With chronic stimulation of the HPA axis there is marked enhancement of AVP production and only a small change in CRH production by parvicellular neurons (Antoni, 1993, Aguilera, 1994). The concentration of pituitary portal AVP is at least one order greater than circulating AVP secreted by the magnocellular neurons in response to osmotic stimulus suggesting the AVP involved in ACTH regulation is provided directly from the posterior pituitary or median eminence, however, this is not clear as there is evidence suggesting AVP is released from the axons of the magocellular neurons as they pass through the internal zone of the median eminence. The AVP may gain access to the pituitary portal circulation through the fenestrated capillaries of the subependymal plexus. (Antoni, 1993, Aguilera, 1994). If this is the case then there is overlap of AVP released in response to osmotic stimuli and ACTH regulation. With chronic stress glucocorticoid levels are elevated and glucocorticoid feedback regulating this increase is impaired so the elevated glucocorticoid levels are maintained. Implicit in this is that AVP levels may also remain elevated because of impaired glucocorticoid feedback. Magnocellular and parvicellular cells in the SON contain type II (glucocorticoid preferring) corticosteroid receptors

suggesting direct action of glucocorticoids on the regulation of AVP (Antoni, 1993, Dinan, 1994). These type II receptors are implicated in the co-ordination of behavioural and endocrine responses to stressful stimuli, particularly the hypothalamic-pituitary-adrenal axis response (Dinan, 1994). In contrast to chronic stress, with chronic osmotic stimulation ACTH secretion is inhibited despite high circulating levels of AVP. This is probably due to diminished parvicellular PVN activity and down-regulation of pituitary AVP receptors (Aguilera, 1994). It stands to reason that the stress that is often an integral part of mental illness alters AVP secretion, increasing vulnerability to impaired control of water and electrolyte balance. In depression it has been established that a significant number of patients hypersecrete cortisol due to overactivity of the hypothalamic-pituitary-adrenal axis (Dinan, 1994). An interesting hypothesis is this hypersecretion of cortisol is due to increased secretion of AVP from the parvicellular neurons. In depression basal serum AVP concentration, the release of AVP in response to osmotic stress and AVP response to apomorphine have all been observed to be decreased and in mania the reverse has been found (Legros et al., 1993). This reflects a blunted response from the magnocellular neurons.

**3.3 AVP action at receptor level.**

There are two principal types of AVP receptors in the human body, V1 and V2. V1 receptors are subclassified as V1a and V1b. V1a are most widespread being found in smooth muscle, myometrium, bladder, adipocytes, hepatocytes, platelets, renal medullary

interstitial cells, vasa recta in the renal microcirculation, epithelial cells in the renal cortical collecting duct, spleen, testis and many CNS structures. V1b receptors seem to occur only in the adenohypophysis. V2 receptors are mainly found in the renal collecting duct system (Rinaman *et al,*. 1995, Jackson, 1996). The affinity of V1b receptors for AVP are one order greater in magnitude than V2 receptors and this may be important for differential activation of these receptors by circulating AVP (Aguilera, 1994). The kidneys are exquisitely sensitive to AVP, with the main antidiuretic function of AVP being mediated via the V2 receptors. The exact function of V1a receptors in the kidney is unclear, except for involvement with prostaglandin synthesis. Under normal conditions the walls of the collecting duct system are impermeable to water allowing the passage of dilute urine. With AVP secretion, water permeability of the collecting duct system is increased. The osmotic gradient between the hypotonic urine and the hypertonic interstitial fluid drives the flux of water from the urine thereby diluting the serum (Johnson *et al*., 1994, Jackson, 1996).

The mechanism of V2 receptor-effector coupling is as follows. The V2 receptor is linked to a stimulatory G-protein, which activates adenyl cyclase. Cyclic adenosine-3.5-monophosphate(cAMP) levels rise activating cAMP-dependent protein kinase A. By an unknown mechanism there is an increased rate of exocytosis of water channel-containing vesicles into the apical membrane of the renal collecting duct cells and a decreased rate of endocytosis of these vesicles from the membrane. This increases the number of active water channels in the membrane thereby increasing water permeability. Urea transporters are also activated although this seems to be a separate system to the water channels as it

is confined to the inner medullary collecting duct, which allows larger osmolality to develop in the inner medullary collecting duct, increasing the urine concentrating ability of the kidney (Jackson, 1996). The V2 receptors also mediate sodium transport mainly in the cortical collecting duct by activation of existing channels and by insertion into the membrane of sodium channel-containing vesicles. Activation of V2 receptors also increase circulating levels of procoagulin factor VIII and von Willebrand factor (Jackson, 1996).

The V1 receptor is also linked to a G-protein. When AVP binds to the receptor, the G-protein mediates activation of phospholipase C, which hydrolyses phosphatidylinositol-4.5-bisphosphate generating inositol-1.4.5-triphosphate (IP3) and diacyl-glycerol (DAG). IP3 binds to receptors on $Ca^{2+}$ channels of intracellular $Ca^{2+}$ stores resulting in $Ca^{2+}$ release. There is also influx of extracellular calcium by an unknown mechanism. The V1 receptor secondly mediates the activation of phospholipase D, which in turn mediates the hydrolysis of other phospholipids to also produce DAG. DAG activates protein kinase C, which phosphorylates proteins that contribute to the biological process. The third process is the stimulation of phospholipase $A_2$, which mobilises arachidonic acid from membrane phospholipids. Arachidonic acid is metabolised to prostaglandins and epoxyeicosatrienoic acids (Jackson, 1996). Prostaglandins limit the antidiuretic effect of AVP (Johnson *et al.*, 1994). V1 receptors mediate vasoconstriction particularly in skin, skeletal muscle, fat, pancreas and thyroid gland and also to a lesser degree gastrointestinal tract, coronary vessels and brain. Furthermore V1 receptors mediate glycogenolysis, platelet aggregation, ACTH release, and growth of smooth muscle cells

and at high concentrations stimulation of uterine and gastrointestinal smooth muscle. (Aguilera, 1994, Jackson, 1996).

**4.0 Physiological changes in the elderly.**

With aging basal arginine vasopressin (AVP) secretion is increased but volume of distribution and clearance is unchanged (Phillips *et al.*, 1984, Johnson *et al.*, 1994). Along with this, AVP secretion in response to osmoreceptor stimulation increases (Lindeman, Van Buren & Raisz, 1960, Helderman *et al.*, 1978). In subjects over 75 years the relationship between plasma AVP and osmolality breaks down and AVP secretion is probably increasingly determined by baroreceptor input. This apparent loss of osmotic regulation of AVP secretion may be due to age related involutional changes in the neurohypohysis (Johnson *et al.*, 1994). This picture is complicated because baroreceptor function is also compromised with aging. Rowe *et al.* (1982) reported there is reduced AVP secretion in response to baroreceptor stimulation. Normally a hypertonic saline infusion increases blood volume, pressure and pulse. The raised pulse and blood pressure dampen AVP secretion in response to the osmolar stimulus. With an age-related defect in baroreceptor mediated input to the hypothalamus this dampening effect is ameliorated, allowing unrestrained response to changes in osmolality. So despite an increase in blood volume and pressure, AVP will be secreted in response to the rising osmolality, resulting in water retention and further hypertension (Rowe *et al.*, 1982).

Other physiological changes associated with aging also place the elderly at risk of developing hyponatraemia. Renal concentrating ability (Lindeman *et al.*, Van Buren & Raisz, 1960, Phillips *et al.*, 1984), glomerular filtration rate and renal blood flow are reduced (Rowe, 1992). The aging kidney has a salt losing tendency which is caused by nephron loss, with increased osmotic load per nephron leading to mild osmotic diuresis (Rowe, 1992). Furthermore there is increased secretion of atrial natriuretic hormone and a less active renin-aldosterone system (Ohashi *et al.*, 1978). The kidneys' ability to regulate salt balance under stress is compounded by similar abnormalities in water balance. The elderly therefore have a blunted capacity to conserve water and excrete concentrated urine (Rowe, 1992). Renal factors are thus also responsible for impaired water and electrolyte control. Moreover, the subjective sensations of thirst are reduced, compromising fluid intake after dehydration (Phillips *et al.*, 1984). The accepted normal range for serum osmolality in the elderly is 260-309 mOsm/l as compared with a range of 281-297 mOsm/l in healthy adults (Hodkinson, 1977).

**4.1 Hyponatraemia in the elderly.**

Hyponatraemia in the elderly is a common phenomenon. Miller *et al.* (1996) found a prevalence of 8% and a two-year incidence of 11.4% in ambulatory geriatric populations. In a nursing home population the prevalence for hyponatraemia was 18% of which 81% were mild (130–134 mmol/l) and the rest moderate (125-129 mmol/l). The one-year incidence was 53% of which 67% were mild, 28% moderate and 5% severe (≤124

mmol/l). (Miller *et al.*, 1995, Miller *et al.*, 1996). A prevalence of 8.6% of serum sodium below 137 mmol/l was reported in an elderly population living at home with no acute illnesses (Caird *et al.*, 1973). In a sample of 120 patients with chronic illnesses of which 75% were older than 65 years, 22.5% of had a serum concentration below 135 mmol/l on three occasions (mean sodium concentration was 120 mmol/l) during a six month period. Of those individuals 75 %were symptomatic albeit with non-specific complaints (Kleinfeld *et al.*, 1979).

**4.2 Complications of hyponatraemia**

Symptoms are more common with hyponatraemia in the setting of normal or increased extracellular volume and are principally due to movement of water into the brain. These symptoms and signs usually occur only when the serum sodium concentration is below 120 mmol/l, or more typically around 112 mmol/l, and they include headache, confusion, restlessness leading to drowsiness, myoclonic jerks and generalised seizures (Tomson, 1994). The brain oedema associated with hyponatraemia can lead to several secondary conditions such as pulmonary oedema, central diabetes insipidus and mellitus, cerebral infarction, cortical blindness, persistent vegetative state, respiratory arrest and coma. Permanent brain damage or death may occur (Fraser & Arieff, 1997). Acute hyponatraemia, occurring in less than 12 hours, is associated with a high mortality rate. In a series of acute hyponatraemia in 14 subjects reported by Arieff *et al.* (1976) the mean sodium concentration was 112 mmol/l and half of them died. They found in chronic

hyponatraemia symptoms were correlated with more severe hyponatraemia, mean sodium concentration of 115 mmol/l vs. a mean sodium concentration of 122 mmol/l in asymptomatic patients. In an animal model symptoms were correlated with the interplay between net increase in brain water vs. loss of brain electrolytes. Even in chronic asymptomatic hyponatraemia there was a significant increase in brain water (Arieff *et al.*, 1976). In one series of seven patients, three died and two suffered permanent paralysis (Ashraf *et al.*, 1981). Central pontine myelinolysis is another complication that is thought to be due to too rapid correction of hyponatraemia. It is seen in experimental animals, but is rare in humans (Ayus *et al.*, 1982, Kovacs & Robertson, 1992, Fraser & Arieff, 1997).

**4.3 Causes of Hyponatraemia.**

Hyponatraemia can occur in three settings of extracellular volume namely normal, decreased or increased (Tomson, 1994). The causes in each of these setting are listed in table 4.

| NORMAL EXTRACELLULAR VOLUME | DECREASED EXTRACELLULAR VOLUME |
|---|---|
| Abnormal AVP release | GIT |
| Vagal neuropathy | Vomiting |
| Deficiency of ACTH | Diarrhoea |
| Hypothyroidism | Haemorrhage |
| Severe potassium depletion | |
| | Kidney |
| SIADH | Osmotic diuresis |
| | Excessive use of diuretics |
| Stress | Adrenocortical insufficiency |
| Surgery | Tubulo-intestinal renal disease |
| Nausea | Unilateral renal artery stenosis |
| | Recovery phase of acute tubular necrosis |
| Major psychiatric illness | |
| Psychogenic polydipsia | |
| Non-osmotic AVP release | |
| Increased sensitivity to AVP | |
| Chlorpropamide | |
| Tolbutamide | **INCREASED EXTRACELLULAR VOLUME** |
| | Heart failure |
| AVP-like substances | Liver failure |
| Oxytocin | Oliguric renal failure |
| DDAVP | Hypoalbuminaemia |
| Unmeasured osmotically active substances stimulating osmotic AVP release | |
| Glucose | |
| Alcohol | |
| Mannitol | |
| Sick cell syndrome | |

**Table 4. Causes of hyponatraemia.** (Tomson, 1994)

## 4.4 Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Hyponatraemia in the elderly is thought most often to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Miller *et al.* (1996) found in 59% of elderly subjects developing hyponatraemia it could be attributed to SIADH (Miller *et al.*, 1996). The criteria for SIADH devised by Bartter and Schwartz (1967) require the presence of hyponatraemia, plasma hypo-osmolality and urine less than maximally dilute.

The following need to be excluded: hypovolaemia, hypotension, renal, adrenal or thyroid insufficiency, congestive cardiac failure, nephrosis, cirrhosis, or other disorders resulting in generalised oedema (Bartter & Schwartz, 1967). This is not necessarily due to inappropriate secretion of AVP, but may be due to erratic secretion of AVP independent of osmoreceptor function, or resetting of the osmostat, or an AVP 'leak', or due to an as yet unidentified antidiuretic substance (Kovacs & Robertson, 1992). Furthermore it may also be due to abnormal renal response to AVP. Raised serum AVP levels do not necessarily result in plasma hypotonicity because in normal individuals this will be counteracted by lack of thirst and reduced fluid intake. To cause hypotonicity, excessive fluid intake accompanies the raised AVP. Converse to SIADH, inadequate AVP secretion or insufficient response by the kidneys results in Diabetes Insipidus. Water conservation is impaired and large volumes of dilute urine are excreted (Jackson, 1996).

## 5.0 Medical conditions associated with SIADH.

There are numerous medical conditions associated with the development of SIADH. These conditions are more prevalent with increasing age and thus in the elderly they often occur in the context of already precarious physiological function. The commonly associated conditions are conveniently divided into five categories: AVP producing tumours; pulmonary diseases; central nervous system disorders; general surgery and drugs (Table 5) (Kovacs & Robertson, 1992). A proportion are idiopathic, especially in the elderly (Miller *et al.*, 1996). The usefulness of the concept of SIADH has been

questioned because many disorders present with a similar biochemical picture but have widely differing aetiologies (Kennedy *et al.*, 1978).

| | | |
|---|---|---|
| **Tumours** | | **Drugs** |
| Bronchogenic Carcinoma | | Chlopropamide |
| Uterine Carcinoma | | Cyclophosphamide |
| Mesothelioma | | Vincristine |
| Proststatic Carcinoma | | Rampril |
| Thymoma | | Lisinopril |
| Lymphoma | | Furosemide |
| Duodenal Carcinoma | | Thiazide |
| Leukaemia | | Morphine |
| Pancreatic Carcinoma | | Barbiturate |
| Nasopharangeal Carcinoma | | NSAID |
| | | Antidepressant |
| **CNS Disease** | | Antipsychotic |
| Mass lesions | Tumours | Carbamazepine |
| | Brain abscess | Lipid lowering agent |
| | Subdural | Nicotine e.g. smoking |
| | Haematoma | |
| Inflammatory disease | Encephalitis | **Other** |
| | Meningitis | AIDS & AIDS related complex |
| | SLE | |
| | Acute intermittent porphyria | |
| Degenerative disease | Guillain Barre | |
| | Spinal cord lesions | |
| Other | Subarachnoid haemorrhage | |
| | Head trauma | |
| | DT's | |
| | Pituitary stalk lesion | |
| | Hydrocephalus | |
| **Pulmonary Disease** | | |
| Infections | Tuberculosis | |
| | Pneumonia | |
| | Aspergillosis | |
| | Empyema | |
| Ventilatory | Acute respiratory failure | |
| | Chronic obstructive airways disease | |
| | Positive pressure ventilation | |
| **General Surgery** | | |

**Table 5. Diseases and Drugs associated with SIADH** (Kovacs & Robertson 1992).

**6.0 Drugs and AVP.**

Drugs are probably the most common cause of SIADH and among those used in psychiatry: carbamazepine, all classes of antidepressants, antipsychotics and anxiolytics have been implicated. However, there are no accurate estimates of incidence because the majority of reports are of single cases, which in itself suggests an idiosyncratic reaction (McAskill & Taylor, 1997). It is thus for example, not possible to compare the incidence of hyponatraemia associated with selective serotonin re-uptake inhibitors (SSRIs) to that of other drugs e.g. tricyclic antidepressants.

The mechanism by which drugs affect vasopressin secretion varies. Some drugs have direct effects on one or more CNS structures that regulate AVP secretion whereas other drug indirectly affect AVP secretion by altering blood volume, blood pressure, pain or nausea. In most cases the mechanism is unknown. Drugs that stimulate vasopressin secretion include vincristine, cyclophosphamide, tricyclic antidepressants, nicotine, epinephrine and high doses of morphine. Lithium enhances secretion of AVP, but inhibits the renal effects. Ethanol, phenytoin, low dose morphine, glucocorticoids, fluphenazine, haloperidol, promethazine all inhibit AVP secretion. Carbamazepine inhibits vasopressin secretion centrally, but promotes water retention by direct action on the kidneys. Non steroidal anti-inflammatory drugs enhance the antidiuretic response to AVP by reducing prostaglandin production thereby removing the inhibitory effects of prostaglandin. (Jackson, 1996).

**6.1 SSRIs, hyponatraemia and AVP.**

There have been numerous case reports in the literature of the association between hyponatraemia and the use of SSRIs. Liu *et al.* (1996) analysed 30 published case reports and 706 cases reported to monitoring bodies and the pharmaceutical industry in North America. They found that 55.7% of cases were 65 years and older; 60.3% were female and the median onset time was 13 days. Withdrawal of SSRIs when reported resulted in correction of the serum sodium (Liu *et al.*, 1996), the mean recovery time after withdrawal was 9.2 days in several cases (reported in 21 of the 30 cases). In all these cases the blood and urine osmolality and sodium concentration, when reported, were compatible with the SIADH. Several subjects had concomitant conditions associated with SIADH and none had other causes of hyponatraemia rigorously excluded according to the criteria of Bartter and Schwartz (1967).

The Australian Adverse Reactions Advisory Committee (ADRAC, 1996) published data from 33 reports of hyponatraemia associated with SSRIs. The age of subjects ranged between 71.5 - 80 years with a 76% female preponderance. Serum sodium levels ranged between 111 – 123 mmol/l (ADRAC, 1996).

The argument for a causal relationship between SSRIs and hyponatraemia is strengthened by reports by Cohen et al., (1990), Jackson *et. al.* (1995) and Flint *et. al.* (1996) of three patients who were rechallenged with a different SSRI and again developed hyponatraemia. However, Staab *et al.* (1990) report rechallenging a 59 year man with the

same SSRI without recurrence of hyponatraemia. This would need further research for clarification. A causal relationship cannot be excluded if a patient did not re-develop hyponatraemia as it could be argued that exposure to a SSRI is protective or sensitising.

Serum fluoxetine and vasopressin levels above normal ranges have been recorded in two elderly women who had developed hyponatraemia (Girault *et al.*, 1997). As the authors suggest, this could be explained by impaired elimination of fluoxetine and impaired control of vasopressin secretion. They go further to suggest a causal relationship between impaired fluoxetine elimination, raised serum fluoxetine and control of vasopressin secretion. If this hypothesis is true then raised serum fluoxetine levels may be predictive of hyponatraemia. The effect of SSRIs on AVP secretion has not been clearly established and a lot of information is contradictory, for example in obsessive compulsive disorder fluoxetine has been noted to decrease AVP synthesis (Legros *et al.*, 1993)

In the literature search conducted no figures were found for the incidence of hyponatraemia in the elderly with mental illness. Pillans and Coulter (1994) calculated the incidence of hyponatraemia associated with fluoxetine based on a number of spontaneous reports received during a four-year post-marketing event monitoring study. These rates were 5.4 per 1000 for patients over 65 years and 8.4 per 1000 women over 65 years (Pillans & Coulter, 1994). In their review Thomas and Verbalis (1995) quote these same figures except tenfold greater i.e. 5.4 per 100 and 8.4 per 100 respectively. As recently highlighted by Bouman *et al.*, (1997) systematic epidemiological and clinical studies are lacking. What is not clear from any of these studies is whether SSRIs affect

AVP secretion, another aspect of AVP regulation or the renal end-organ effects of AVP. Most information about hyponatraemia associated with SSRIs has been case studies and anecdotal evidence. This kind of evidence identifies the presence of the problem and allows only speculation because information is incomplete and confounding variables are never excluded. These reports of hyponatraemia need to be put in the context of widespread, mostly uneventful use of SSRIs.

## 7.0 Psychiatric illnesses, hyponatraemia and AVP.

Psychiatric morbidity is also associated with hyponatraemia. A prevalence of 10.5% was recorded in one study of a psychiatric inpatient population. Of these, 75% had schizophrenia and the remainder included all other psychiatric illnesses except the neuroses (Ohsawa *et al.*, 1992). Earlier age of onset of psychiatric disorder, duration of psychiatric disorder, and prolonged admission were associated with a higher incidence of hyponatraemia. The AVP secretion in response to osmolar stimulation was reduced in patients with schizophrenia indicating abnormal function of the AVP system (Ohsawa *et al.*, 1992). A case of SIADH occurring during a psychotic episode in a patient who was taking no medications and had no evidence of other conditions associated with SIADH was reported by Dubovsky *et al.*,(1973). In this case the SIADH recurred during a second psychotic episode and resolved with remission of the psychosis. It has been found that in patients with Alzheimer's disease the control of AVP release is impaired with CNS and CSF AVP levels being raised. Alterations in AVP secretion have also been observed in

anorexia, obsessive compulsive disorder, obesity, depression, mania and alcoholism (Demitrack *et al.*, 1989, Legros *et al.*, 1993, Rinaman *et al.*, 1995). Most of these reports are case studies or involve small samples and these findings are cannot be generalised to other people with mental illness. They do serve to illustrate that mental illness can affect AVP secretion and function. It must also be borne in mind that most people with mental illness probably have normal AVP secretion and function.

**8.0 Sex hormones, AVP and hyponatraemia.**

Premenopausal women have been noted to be at substantially greater risk of dying or developing permanent brain damage from symptomatic hyponatraemia than either postmenopausal women or men of any age. Female sex hormones have an inhibitory effect on brain $Na^+$-$K^+$ ATPase pump action. Female sex hormones have been shown to affect plasma levels of AVP. In rats plasma AVP levels vary with stages of the female menstrual cycle. Orchidectomy in male rats is associated with increased AVP levels and if testosterone is administered the AVP levels fall (Fraser & Arieff, 1997). By this argument the low levels of oestrogen and progesterone in elderly women means sex hormones should not increase their risk of developing hyponatraemia or its complications.

**9.0 Statement of the problem.**

In summary, there are two AVP systems in the CNS, the magnocellular and parvicellular systems both situated predominantly in the hypothalamus (diagram 1.). The former responds to osmotic and baroreceptor stimuli by releasing AVP from the neurohypophysis into the peripheral circulation. The latter innervates the CNS, especially the limbic area. An important group of neurons are the CRH neurons that secrete CRH and AVP from the median eminence into the pituitary portal system resulting in ACTH release. AVP in the limbic area seems to be involved in the complex process of emotional evaluation of incoming information. The 'magnocellular' and 'parvicellular' systems probably are under separate control although there is evidence of overlap.

AVP exerts a strong action on the renal collecting duct increasing water re-absorption. Maintenance of water balance depends on many processes including renal physiology, AVP, thirst sensation and blood pressure all working synergistically. Defects in one process are normally compensated for. In the elderly physiological changes in the kidney and hypothalamus mean several of the processes controlling water balance are compromised making them vulnerable to an imbalance.

The elderly are more likely to develop medical illnesses and receive drugs that alter AVP secretion directly or indirectly. This is confirmed by the higher rate of hyponatraemia found in this population. The elderly with mental illnesses will have these risk factors as well as the added risk of the mental illness altering AVP secretion. Depression with its

altered glucocorticoid secretion particularly suggests involvement of AVP secretion. The observed relationship between SSRIs and hyponatraemia in the elderly strengthens the hypothesis that they are a group vulnerable to defective AVP secretion.

The aims of the first part of this paper are to report the published cases of hyponatraemia occurring whilst using SSRIs from the United Kingdom and specifically focus on cases in people 60 years and older. Secondly to re-analyse all case reports in the literature looking only at this population. The third aim was to investigate whether dysregulation of vasopressin function in the elderly using SSRIs is a sporadic or usual phenomenon.

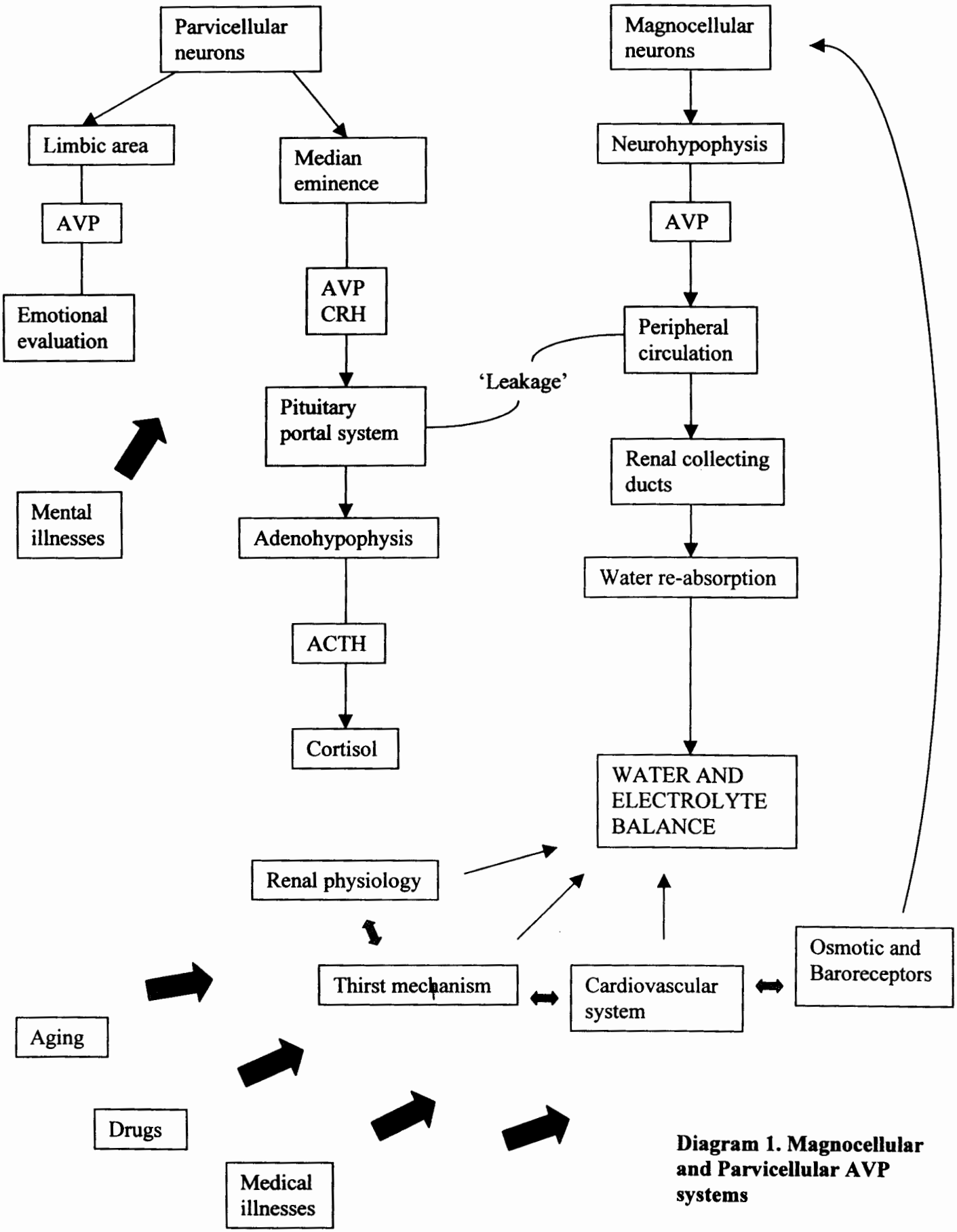


**Diagram 1. Magnocellular and Parvicellular AVP systems**

# METHODS

## Part 1

A literature search was done using Medline to identify case reports of hyponatraemia associated with SSRI use in patients 60 years and older. There were 46 cases identified but the information reported was often limited (Hwang & McGraw, 1989, Cohen *et al.*, 1990, Gommans & Edwards, 1990, Marik *et al.*, 1990, Goddard & Paton, 1992, Blacksten & Birt, 1993, Chua & Vong, 1993, Crews *et al.*, 1993, Kazal *et al.*, 1993, McHardy, 1993, Ball & Hertzberg, 1994, Druckenbrod & Mulsant, 1994, Llorente *et al.*, 1994, Pillans & Coulter, 1994, Ayonrinde *et al.*, 1995, Jackson *et al.*, 1995, Leung & Remick, 1995, Taylor & McConnell, 1995, Thornton & Resch, 1995, ADRAC, 1996, Flint *et al.*, 1996, Kessler & Sameuls, 1996, Ng & Alderman, 1996, Robinson *et al.*, 1996, Ten Holt *et al.*, 1996, Voegeli & Baumann, 1996, Girault *et al.*, 1997) (Table 6). In each case the following information was collected: age, sex, dose of SSRI, time to detection of hyponatraemia, lowest serum sodium level recorded, and time to recovery of serum sodium.

| Author | Age | Sex | SSRI | Dose (mg) | Time to detection | Serum Na (mmol/l) | Serum Osm (mOsm/l) | Urine Osm (mOsm/l) | Urine Na (mmol/l) | Time to recovery | Reported symptoms |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hwang & Magraw 1989 | 75 | M | Fluoxetine | 20 | 10 | 126 | 264 | 417 | - | 10 | |
| Cohen *et al.* 1990 | 82 | F | Fluoxetine | 20 | 3 | 125 | 265 | - | 74 | 7 | |
| Cohen *et al.* 1990 | 79 | F | Fluoxetine | 20 | 42 | 129 | - | - | - | 5 | |
| Cohen *et al.* 1990 | 79 | F | Fluoxetine | 20 | 5 | 128 | - | - | - | 5 | |
| Cohen *et al.* 1990 | 84 | F | Fluoxetine | 40 | 21 | 124 | 264 | - | 54 | 14 | |
| Cohen *et al.* 1990 | 85 | M | Fluoxetine | 20 | 7 | 126 | 272 | - | 84 | 14 | |
| Gommans & Edwards 1990 | 75 | F | Fluoxetine | 20 | 12 | 116 | 242 | 337 | 91 | 6 | Drowsiness, confusion |
| Goddard & Paton 1992 | 69 | F | Paroxetine | 20 | 16 | 126 | - | - | - | 2 | Drowsiness, lethargy |
| Blacksten & Birt 1993 | 92 | F | Fluoxetine | 20 | 13 | 98 | 214 | 465 | 114 | 8 | Weakness, loss of appetite, lethargy |
| Chua & Vong 1993 | 78 | F | Paroxetine | - | 5 | 115 | 256 | 369 | - | 10 | Confusion |
| Chua & Vong 1993 | 76 | M | Paroxetine | - | 7 | 112 | 246 | 292 | - | 4 | Confusion |
| Crews *et al.* 1993 | 73 | M | Sertraline | 50 | 5 | 118 | 251 | 511 | 33 | - | Collapse |
| Kazal *et al.* 1993 | 83 | F | Fluoxetine | 20 | 6 | 124 | 256 | 573 | 85 | 13 | Confusion, weakness |
| Marik 1993 | 60 | F | Fluoxetine | - | 112 | 106 | 225 | 452 | 50 | 14 | Drowsiness, confusion |
| McHardy 1993 | 70 | F | Fluvoxamine | 100 | 5 | 114 | 239 | 392 | - | 6 | Confusion |
| Ball *et al.* 1994 | 74 | F | Fluoxetine | 20 | 14 | 116 | - | - | 42 | 14 | |
| Druckenbord & Mulsant 1994 | 83 | F | Fluoxetine | 40 | 65 | 109 | 242 | 530 | 46 | 28 | Agitated |
| Llorente *et al.* 1994 | 92 | M | Sertraline 50 | 50 | 5 | 122 | 260 | 361 | 59 | 7 | |
| Pillans & Coulter 1994 | 76 | F | Fluoxetine | 20 | 13 | 116 | 242 | 337 | 91 | 22 | Drowsiness, confusion |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pillans & Coulter 1994 | 81 | F | Fluoxetine | 20 | 8 | 128 | - | - | - | 4 | |
| Pillans & Coulter 1994 | 76 | F | Fluoxetine | 20 | 19 | 120 | - | - | - | - | Lethargy |
| Pillans & Coulter 1994 | 88 | F | Fluoxetine | 20 | 15 | 121 | 253 | 456 | - | - | |
| Pillans & Coulter 1994 | 68 | F | Fluoxetine | 20 | 60 | 120 | - | - | - | - | Confusion |
| Pillans & Coulter 1994 | 87 | F | Fluoxetine | 20 | 42 | 114 | - | - | - | 21 | |
| Pillans & Coulter 1994 | 84 | F | Fluoxetine | 20 | 13 | 117 | - | - | - | 10 | |
| Ayonrinde *et al.* 1995 | 67 | F | Paroxetine | 20 | 7 | 114 | 232 | 372 | 49 | 9 | Lethargy, weakness, loss of appetite |
| Jackson *et al,* 1995 | 77 | F | Fluoxetine | 20 | 12 | 104 | 216 | 334 | - | - | Confusion |
| Jackson *et al.* 1995 | 77 | F | Sertraline | 50 | 14 | 126 | 246 | 418 | - | 3 | |
| Leung & Remick 1995 | 87 | M | Sertraline | 50 | 15 | 118 | - | - | - | 14 | Dizziness, nausea & vomiting collapse |
| Taylor & McConnell 1995 | 89 | F | Sertraline | 50 | 35 | 112 | 236 | 222 | 51 | 14 | Confusion |
| Taylor & McConnell 1995 | 83 | F | Fluoxetine | 20 | 35 | 120 | - | - | - | 14 | |
| Taylor & McConnell 1995 | 73 | F | Fluoxetine | 20 | 14 | 118 | 252 | 314 | - | 7 | Dizziness |
| Thorton & Resch 1995 | 60 | M | Sertraline | 50 | 5 | 126 | 256 | 389 | - | - | Confusion |
| Thorton & Resch 1995 | 72 | F | Sertraline | 75 | 4 | 105 | 217 | 393 | - | - | Confusion |
| ADRAC 1996 | 77 | F | Sertraline | 50 | 5 | 121 | 253 | 482 | - | 7 | Confusion |
| Flint *et al.* 1996 | 78 | F | Paroxetine | 10 | 7 | 125 | - | - | - | 10 | |
| Flint *et al.* 1996 | 78 | F | Fluoxetine | 20 | 140 | 118 | 255 | 705 | 23 | 14 | Dizziness, weakness, lethargy |
| Kessler & Sameuls 1996 | 82 | F | Sertraline | 50 | 3 | 123 | - | 373 | 36 | 6 | |
| Ng & | 81 | M | Sertraline | 50 | 4 | 120 | 262 | 718 | - | - | Confusion |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alderman 1996 | | | | | | | | | | | |
| Ng & Alderman 1996 | 76 | F | Fluoxetine | 60 | 28 | 118 | 244 | 612 | 13 | - | Weakness, loss of appetite |
| Robinson *et al.* 1996 | 70 | M | Sertraline | 50 | 84 | 129 | ↓ | ↑ | - | - | |
| Ten Holt *et al.* 1996 | 78 | F | Fluoxetine | 20 | 42 | 103 | - | 209 | - | - | Drowsiness, stupor, weakness |
| Ten Holt *et al.* 1996 | 73 | F | Fluoxetine | 20 | 5 | 110 | - | 247 | - | - | Lethargy, dyspnoea |
| Voegli & Bauman 1996 | 73 | F | Citalopram | 20 | 7 | 128 | - | - | - | 3 | |
| Girault *et al.* 1997 | 70 | F | Fluoxetine | 20 | 30 | 106 | 205 | 420 | 13 | 8 | Drowsiness, confusion |
| Girault *et al.* 1997 | 81 | F | Fluoxetine | 20 | 48 | 104 | - | - | 9 | 13 | Weakness, confusion |

**Table 6. Cases of hyponatraemia associated with SSRI use in the elderly reported in the literature.**

Computerised records were requested of adverse drug reactions to SSRIs from the Committee on Safety of Medicines, which is the official monitoring body that collects spontaneous reports of side effects of medications from prescribing doctors in the UK. Records were requested on fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine. The records included all reports up until 3/12/1996. The following data was requested on each drug: age, sex, dose of SSRI, time to detection of hyponatraemia, lowest serum sodium level recorded, and time to recovery of serum sodium. Data was excluded if the age or sex of the patient was not given or if they were under 60 years of age. There were 257 cases of hyponatraemia associated with SSRIs during this period. Of these 32 were excluded because of incomplete data, 23 were under 60 years old, and 202 cases were suitable for analysis.

Since the data is retrospective and often incomplete, simple descriptive analysis was initially performed using Microsoft Excel. Columns were analysed separately so that the sample size for each column was the number of cases in which the relevant information was available. When comparisons were made of means a two-tailed T-test with unequal variance was performed. The Chi squared test was performed to compare contribution made to the sample by females and males.

**Part 2**

Subjects were identified by clinicians working in the Department of Mental Health for Older People, Homerton Hospital, London. This research project was approved by the East London and the City Health Authority Research Ethics Committee. To be included subjects had to be 65 years and older and about to be started on sertraline for a depressive illness. It was decided to use sertraline on all patients requiring a new SSRI during the time of the study to limit confounding variables and it was already a preferred agent of most clinicians at the time. If their baseline serum sodium concentration was abnormal they were excluded. The decision to treat was made by the responsible clinician. Written consent was taken from subjects and they were given an information sheet about the study. Nine patients were started on sertraline during the period April to November 1997. Three patients were excluded from the trial. One refused to give consent, one was demented and thus unable to give consent and the third patient took an overdose during the first week of treatment. Medical illnesses, psychiatric illnesses, medication, smoking and blood pressure were recorded. Prior to the first dose of sertraline, blood samples were taken by venesection in the cubital fossa by the author and a urine sample was obtained immediately after blood sampling. These samples were analysed for serum electrolytes, urea, creatinine, protein, urate, glucose, thyroid functions, osmolality and urine sodium and osmolality in the Chemical Pathology laboratory, Homerton Hospital, London. Serum and urine sodium concentrations were determined using the Olympus AU600, an automated instrument using ion selective electrodes. Serum and urine sodium concentrations were determined by the Osmomat, an automated instrument detecting

freezing point with an osmometer. These tests were done to establish baseline sodium and osmolality values and to identify other conditions that may cause hyponatraemia according to Bartter and Schwartz (1967). Sertraline 50 milligrams, the recommended starting dose, was then prescribed. Between days 14 and 21 of treatment blood and urine samples were again taken and analysed for serum sodium concentration, serum osmolality, urine sodium and urine osmolality. Two subjects' sample were not completely analysed by the laboratory and had to be repeated. In one the repeat sample was within the 21 day period, the other was not.

Results were then analysed looking specifically for indicators of altered control of vasopressin secretion i.e. hyponatraemia in the context of serum hypo-osmolality and urine less than maximally dilute. The serum and urine sodium concentration and osmolality prior to and during sertraline treatment was compared using a two-tailed t-test for paired data.

# RESULTS

## Part 1

In the published case reports of patients 60 years and older developing hyponatraemia whilst using SSRIs, the mean age was 77.6 years with a standard deviation of ± 7.2 (Table 7). The mean time to detection was 22.2 days, the range being 3-140 days. However the mode was only 5 days. The lowest recorded serum sodium was 98mmol/l with a mean of 117.8 mmol/l and the mean time to normalisation of serum sodium was 10.2 days. In only three cases (6.5%) was the dose of SSRI greater that the recommended starting dose. Of the cases, 80% were female.

| | **Mean ± SD** | **Mode** | **Range** |
|---|---|---|---|
| **Age (years) n=46** | 77.6 ± 7.2 | | 60 – 92 |
| **Time to detection (days) n=46** | 22.2 ± 28.4 | 5 | 3 – 140 |
| **Time to normalisation of serum sodium (days) n=34** | 10.2 ± 5.8 | 14 | 2 – 28 |
| **Lowest serum sodium (mmol/l) n=46** | 117.8 ± 8.0 | | 98 – 129 |
| **Sex male=9 females=37** | ratio1:4 | | |

**Table 7. Results of analyses of all published case reports of hyponatraemia associated with SSRI use.**

The 202 cases reported to the Committee on Safety of Medicines had a mean age of 78.0 years with a standard deviation of ±8 years (Table 8). The mean time to detection was 21

days, the range was 1-253 days and the mode 7 days. The mean time to normalisation of serum sodium upon cessation of SSRI was 9 days. As in the published case reports, the lowest recorded serum sodium concentration was 98 mmol/l and the mean was 118.0 mmol/l (Table 2). In this group, 74% of cases were female. In 31 cases (15%) the dose of SSRI was greater than the recommended starting dose.

| | **Mean ± SD** | **Mode** | **Range** |
|---|---|---|---|
| **Age (years) n=202** | 78.0 ± 8.0 | | 60 – 98 |
| **Time to detection (days) n=104** | 21.0 ± 40.0 | 7 | 1 – 253 |
| **Time to normalisation of serum sodium (days) n=72** | 9.0 ± 7.0 | 2 | 1 – 32 |
| **Lowest serum sodium (mmol/l) n=117** | 118.0 ± 7.0 | | 98 – 133 |
| **Sex male=53 females=149** | Ratio 1:2.8 | | |

**Table 8. Results of analyses of data from the Committee on Safety of Medicines of hyponatraemia associated with SSRI use in the United Kingdom.**

The data from the published case reports is very similar to the data from the Committee on Safety of Medicines. The latter is a much larger group and therefore has greater power, so this group was used for further analysis. The data were re-analysed comparing a younger group, 60-69 years, to an older group 70-98 years; females to males; and finally the two age groups were further divided by sex comparing the sexes with themselves and each other.

Table 9. shows the comparison of the younger group, 60-69 years, to the older group, 70-98 years.

| | | 60 – 69 years (± SD) n=31 | ≥70 years (± SD) n=171 | P value |
|---|---|---|---|---|
| **Sex ratio:** | **Female:Male**<br>**% Female** | 1.6:1<br>61% | 3.2:1<br>76% | 0.09 |
| **Age:** | **Mean** (years) n= 170 | 66 ± 3 | 80 ± 6 | |
| **Time to detection:** | **Mean** (days) n=104<br>**Mode** (days)<br>**Range** (days) | 40.4 ± 66.4<br>10.0<br>2 - 253 | 17.5 ± 31.8<br>7.0<br>1 – 229 | 0.19 |
| **Time to normalisation:** | **Mean** (days) n=72<br>**Mode** (days)<br>**Range** (days) | 7.7 ± 4.8<br>8.0<br>1 - 16 | 9.2 ± 7.1<br>2.0<br>1 - 32 | 0.35 |
| **Lowest Sodium:** | **Mean** (mmol/l) n=117<br>**Mode** (mmol/l)<br>**Range** (mmol/l) | 119.6 ± 8.8<br>123.0<br>103.0 –131.0 | 117.4 ± 7.2<br>118.0<br>98.0 – 133.0 | 0.37 |

**Table 9. Comparison of age groups 60 - 69 and 70 - 98 years.**

In the younger group 61% of the sample were female and 76% in the older group were female (Chart 1).

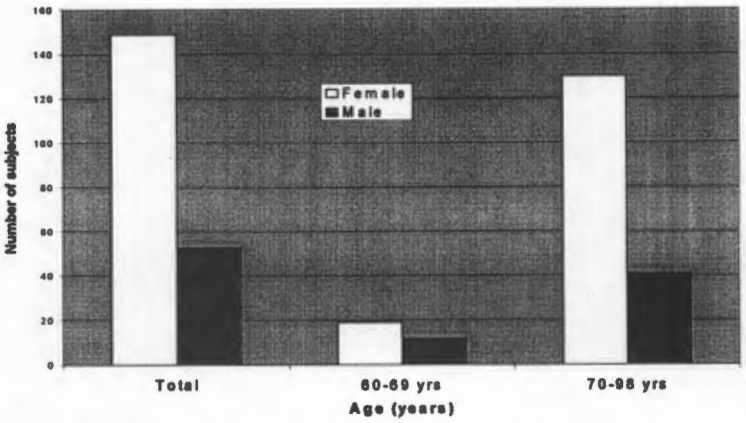


**Chart 1. Sex distribution in two age groups**

The mean of the time to detection was greater in the in the younger group (p=0.032), but the modes were similar. Due to the difference in variance the difference in means was not statistically significant (p =0.19).

The means of the recovery time were not significantly different in the two groups (p=0.35), although the mode was lower in the older group.

There was no significant difference in the means of the lowest sodium concentrations between the two age groups (p=0.37). The mean sodium concentrations in both groups were in the severe range.

| | | Female (n=149) | Male (n=53) | P value |
|---|---|---|---|---|
| **Age:** | **Mean** (years) | 78 ± 7.5 | 76.4 ± 8.6 | 0.20 |
| **Time to detection:** | **Mean** (days)<br>**Mode** (days)<br>**Range** (days) | 17.7 ± 38.2<br>7<br>1-253 | 32.0 ± 43<br>7<br>2-178 | 0.15 |
| **Time to normalisation:** | **Mean** (days)<br>**Mode** (days)<br>**Range** (days) | 9.1 ± 6.5<br>14<br>1-32 | 8.5 ± 7.7<br>2<br>1-32 | 0.79 |
| **Lowest Sodium:** | **Mean** (mmol/l)<br>**Mode** (mmol/l)<br>**Range** (mmol/l) | 117.2 ± 7.3<br>119.0<br>98-133 | 119.3 ± 7.8<br>122.0<br>103-130 | 0.21 |

**Table 10. Comparison of female and male subjects**

Comparing the data for females to males, there was no significant difference in their ages (p=0.20) (Table 10).
The apparently longer time to detection in males did not reach statistical significance (p=0.15). The recovery time was similar (p=0.79).

There was no significant difference between the means of the lowest sodium concentrations between females and males (p=0.21).

| | | Female 60-69yrs (n=19) | Male 60-69yrs (n=12) | Female 70-98yrs (n=130) | Male 70-98yrs (n=41) |
|---|---|---|---|---|---|
| **Age:** | **Mean** (years) | 66.4 ± 2.5 | 64.7 ± 2.9 | 79.9 ± 6.4 | 79.8 ± 6.4 |
| **Time to detection:** | **Mean** (days) | 49.2 ± 87.0 | 31.5 ± 41.0 | 14.2 ± 27.4 | 32.3 ± 45.2 |
| | **Mode** (days) | N/A | N/A | 7 | 7 |
| | **Range** (days) | 2-251 | 6-124 | 1-229 | 2-178 |
| **Time to normalisation:** | **Mean** (days) | 8.3 ± 4.4 | 7.0 ± 5.6 | 9.2 ± 6.8 | 9.2 ± 8.6 |
| | **Mode** (days) | N/A | N/A | 14 | 2 |
| | **Range** (days) | 3-13 | 1-13 | 1-32 | 2-32 |
| **Lowest Sodium:** | **Mean** (mmol/l) | 120.7 ± 8.3 | 118.4 ± 9.7 | 116.9 ± 7.2 | 119.7 ± 7.2 |
| | **Mode** (mmol/l) | N/A | N/A | 118 | 122 |
| | **Range** (mmol/l) | 108-131 | 103-130 | 98-133 | 103-130 |

**Table 11. Comparison of sexes and two age groups**

| | Male 60-69 vs 70-98 yrs | Female 60-69 vs 70-98 yrs | Male 60-69 vs Female 60-69yrs | Male 70-98 vs Female 70-98 yrs |
|---|---|---|---|---|
| **Age** | **N/A** | **N/A** | **0.09** | **0.99** |
| **Detection** | **0.97** | **0.29** | **0.61** | **0.14** |
| **Recovery** | **0.51** | **0.61** | **0.66** | **0.99** |
| **Sodium** | **0.74** | **0.24** | **0.61** | **0.12** |

**Table 11. P values of comparison of sexes and two age groups**

Looking at the data split into the two age groups and sexes (Tables 10&11), there were no significant differences in age (p=0.09), detection time (p=0.61), recovery time (p=0.66), or sodium concentration (p=0.61) in the younger group when comparing females to males. In the older group, there were also no significant differences in age

(p=0.99), detection time (p=0.14), recovery time (p=0.99) or sodium concentration (p=0.12).

Comparing the younger females to the older females, there were no significant differences in the detection time (0.29), recovery time (p=0.61) or sodium concentration (p=0.24). Comparing the younger male group to the older male group, there were no significant differences in detection time (p=0.97), recovery time (p=0.51) or sodium concentration (p=0.74).

The sample was again divided using the mean age as the dividing point. The younger group was now comprised of people 60-78 years old and the older group 79-98 years Table 13). Again the female preponderance remained with women making up 77% and 71% of the two age groups respectively. There were no significant differences between the two age groups in recovery time (p=0.45), or sodium concentration (p=0.65). Hyponatraemia was detected significantly earlier in the older group (p=0.03).

| | | 60–78 years (± SD) n=110 | 79-98 years (± SD) n=92 | P value |
|---|---|---|---|---|
| **Sex ratio:** | **Female:Male**<br>**% Female** | 2.4<br>77% | 3.4<br>71% | 0.31 |
| **Age:** | **Mean** (years) n=202 | 71.8 ± 4.6 | 84.8 ± 4.2 | |
| **Time to detection:** | **Mean** (days) n=104<br>**Mode** (days)<br>**Range** (days) | 28.1 ± 51.8<br>7.0<br>1-253 | 12.7 ± 12.7<br>7.0<br>1-72 | 0.03* |
| **Time to normalisation:** | **Mean** (days) n=71<br>**Mode** (days)<br>**Range** (days) | 9.3 ± 8.2<br>3.0<br>1-32 | 8.2 ± 5.4<br>14.0<br>1-20 | 0.45 |
| **Lowest Sodium:** | **Mean** (mmol/l) n=116<br>**Mode** (mmol/l)<br>**Range** (mmol/l) | 117.4 ± 8.2<br>118.0<br>98-133 | 118.1 ± 6.5<br>119.0<br>103-129 | 0.65 |

**Table 13. Comparison of age groups 60 - 78 and 79 - 98 years.**

When comparing the males in the two age groups (Tables 13&14), there were no significant differences in detection time (p=0.66), recovery time (p=0.76), or sodium concentration (p=0.30). The same held true for the females with detection time (p=0.11), recovery time (p=0.45) and sodium concentration (p=0.80) not significantly different.

The younger female group did not differ from the younger male group in age (p=0.16), detection time (p=0.54), recovery time (p=0.77) or sodium concentration (p=0.53). Similarly the older female group did not differ from the male group in age (p=0.62), detection time (p=0.23), recovery time (p=0.84) or sodium concentration (p=0.06).

| | | Female 60-78yrs (n=78) | Male 60-78yrs (n=32) | Female 79-98yrs (n=71) | Male 79-98yrs (n=21) |
|---|---|---|---|---|---|
| **Age:** | **Mean** (years) | 72.3 ± 4.2 | 70.7 ± 5.4 | 84.6 ± 4.3 | 85.1 ± 3.9 |
| **Time to detection:** | **Mean** (days) | 25.3 ± 54.1 | 34.1 ± 47.6 | 10.8 ± 8.3 | 25.7 ± 26.8 |
| | **Mode** (days) | 2.0 | 7.0 | 7.0 | N/A |
| | **Range** (days) | 1-253 | 2-178 | 1-33 | 4-72 |
| **Time to normalisation:** | **Mean** (days) | 9.7 ± 7.2 | 8.8 ± 8.7 | 8.3 ± 5.5 | 7.8 ± 5.5 |
| | **Mode** (days) | 8.0 | 3.0 | 14.0 | 8.0 |
| | **Range** (days) | 1-32 | 1-32 | 1-20 | 2-18 |
| **Lowest Sodium:** | **Mean** (mmol/l) | 117.0 ± 7.9 | 118.5 ± 8.9 | 117.4 ± 6.7 | 121.1 ± 4.4 |
| | **Mode** (mmol/l) | 118.0 | 130.0 | 119.0 | 118.0 |
| | **Range** (mmol/l) | 98-133 | 103-130 | 103-129 | 116-128 |

**Table 14. Comparison of sexes and two age groups**

| | Male 60-78 vs 79-98 yrs | Female 60-78 vs 79-98 yrs | Male 60-78 vs Female 60-78 yrs | Male 79-98 vs Female 79-98 yrs |
|---|---|---|---|---|
| **Age** | **N/A** | **N/A** | **0.16** | **0.62** |
| **Detection** | **0.66** | **0.11** | **0.54** | **0.23** |
| **Recovery** | **0.76** | **0.45** | **0.77** | **0.84** |
| **Sodium** | **0.30** | **0.80** | **0.53** | **0.06** |

**Table 15. P values of comparison of sexes and two age groups**

Symptoms were reported in 29 of the 46 case reports (Table 16). Confusion, weakness, lethargy, and drowsiness were most frequently reported. In the cases from the Committee on Safety of Medicines, symptoms were poorly reported, however, there were cases of seizures, falls and three fatalities.

| Symptom | No. of reports |
|---|---|
| Confusion | 16 |
| Weakness | 7 |
| Lethargy | 6 |
| Drowsiness | 6 |
| Dizziness | 3 |
| Loss of appetite | 3 |
| Collapse | 2 |
| Stupor | 2 |
| Agitation | 1 |
| Dyspnoea | 1 |
| Nausea & vomiting | 1 |

**Table 16. Symptoms reported in 29 out of 46 published case reports.**

**Part 2**

The cases that were prospectively monitored upon starting sertraline will be presented individually.

***Subject 1:***

An 83 year man presented with a Major Depressive Episode. Four months previously he had a stroke. He was receiving treatment for paroxysmal atrial flutter, iron deficiency anaemia and benign prostrate hypertrophy. At the time of starting sertraline he was taking aspirin, ranitidine, lactulose, ferrous sulphate, ibuprofen, lofepramine, senna and vitamin C. He had been receiving these drugs for several months. The lofepramine was stopped when the sertraline was commenced. No other new drugs were commenced during the two week monitoring period. He smoked 15 cigarettes daily. Prior to commencing

sertraline his serum potassium, creatinine, total protein, albumin, urate, glucose, and thyroid function tests were normal. His urea was raised, 8.7 mmol/l (2.0-6.6 mmol/l). His blood pressure was 155/90. At 14 days follow-up his blood pressure was 150/70, and his potassium and creatinine remained normal. His urea was 8.2 mmol/l. His urine and serum sodium and osmolality are presented in the table below (Table 17). These were essentially unchanged.

| | 1st Sample | 2nd Sample – day 14 |
|---|---|---|
| Serum sodium | 134 mmol/l | 136 mmol/l |
| Serum osmolality | 297 mOsm/l | 301 mOsm/l |
| Urine sodium | 95 mmol/l | 127 mmol/l |
| Urine osmolality | 683 mOsm/l | 739 mOsm/l |

**Table 17. Results of subject 1.**

***Subject 2:***

A 73 year woman presented with a Major Depressive Disorder with somatisation. She had a background history of breast cancer and tuberculosis both of which she was no longer receiving treatment for. She had insulin dependent diabetes, arthritis, hypertension and peptic ulcer disease. At the time of commencing sertraline she was also taking atenolol, frusemide, aspirin, ranitidine, gaviscon, insulin, lorazepam and senna. Three days after commencing sertraline she was prescribed diclofenac sodium and misoprosol by her general practitioner. She was a non-smoker. Prior to commencing sertraline her serum potassium, urea, creatinine, total protein, albumin, urate, glucose, and thryroid function tests were normal. Her blood pressure was 110/70. At 14 days follow-up her blood pressure was 120/70, and her potassium, urea and creatinine remained normal. Her

urea was slightly raised, 7.1 mmol/l. Her urine and serum sodium and osmolality are presented in the table below (Table 18). There were no significant changes.

| | 1st Sample | 2nd Sample – day 14 |
|---|---|---|
| Serum sodium | 137 mmol/l | 136 mmol/l |
| Serum osmolality | 310 mOsm/l | 303 mOsm/l |
| Urine sodium | 68 mmol/l | 151 mmol/l |
| Urine osmolality | 619 mOsm/l | 719 mOsm/l |

**Table 18. Results of subject 2.**

***Subject 3:***

A 76 year man presented with a Major Depressive Episode with somatisation. He was a non-smoker. He was taking digoxin, frusemide and captopril for atrial fibrillation, congestive cardiac failure and hypertension, all of which had been started in the prior few months. No new drugs were commenced during the two week monitoring period. In his initial blood sample his potassium, creatinine, total protein, albumin, urate, and thyroid function tests were normal. His urea was elevated a 10.6 mmol/l in the first sample and 9.4 mmol/l in the second sample. His glucose was 8.5 mmol/l. The potassium and creatinine were unchanged in the second sample. His blood pressure was 160/95 and 160/100 respectively. His urine and serum sodium and osmolality are presented in the table below (Table 19). No significant changes occurred.

| | 1st Sample | 2nd Sample – day 14 |
|---|---|---|
| Serum sodium | 140 mmol/l | 141 mmol/l |
| Serum osmolality | 308 mOsm/l | 306 mOsm/l |
| Urine sodium | 145 mmol/l | 221 mmol/l |
| Urine osmolality | 1040 mOsm/l | 972 mOsm/l |

**Table 19. Results of subject 3.**

***Subject 4:***

A 76 year woman presented with a long standing history of Depressive Disorder with generalised anxiety and somatisation. She was a non-smoker. Her medical problems were hypertension, arthritis, and renal cysts. She was taking alprazolam, propranalol and thioridazine at the time of commencing sertraline. No other drugs were commenced during her monitoring period. In her first blood sample the potassium, creatinine, total protein, albumin, urate and thyroid function tests were normal. The glucose was raised at 9.4 mmol/l and urea at 6.9 mmol/l. Her blood pressure was 170/70 prior to commencing sertraline and 140/80 on day 21. Urine and blood samples were taken on four occasions, but on two of these the data was incomplete. Her urine and serum sodium and osmolality are presented in the table below (Table 20). There were no significant changes.

| | 1st Sample | 2nd Sample – day 12 | 3rd Sample – day 21 | 4th Sample – day 56 |
|---|---|---|---|---|
| Serum sodium | 137 mmol/l | 137 mmol/l | 137 mmol/l | 137mmol/l |
| Serum osmolality | 301 mOsm/l | | | 305 mOsm/l |
| Urine sodium | 65 mmol/l | | | 152 mmol/l |
| Urine osmolality | 895 mOsm/l | | 821 mOsm/l | 631 mOsm/l |

**Table 20. Results of subject 4.**

***Subject 5:***

An 80 year woman presented with a Major Depressive episode. She had a background history of breast cancer 20 years previously for which she was no longer receiving treatment. She had a hiatus hernia, asthma and hypothyroidism. Her medication prior to commencing sertraline was thyroxine, aspirin and salbutamol. She was a non-smoker. Initially her serum potassium, creatinine, total protein, albumin, urate and thyroid

function tests were normal and her blood pressure was 150/90. Her urea was 7.3 mmol/l and glucose was 7.8 mmol/l both being marginally raised. At second testing, the laboratory omitted to do serum osmolality and the sample was repeated on day 21.Her urine and serum sodium and osmolality are presented in the table below (Table 21). Again no changes were significant.

| | 1st Sample | 2nd Sample – day 14 | 3rd Sample – day 21 |
|---|---|---|---|
| Serum sodium | 138 mmol/l | 138 mmol/l | 138 mmol/l |
| Serum osmolality | 298 mOsm/l | | 298 mOsm/l |
| Urine sodium | 46 mmol/l | 31 mmol/l | 40 mmol/l |
| Urine osmolality | 610 mOsm/l | 486 mOsm/l | 707 mOsm/l |

**Table 21. Results of subject 5.**

***Subject 6:***

A 76 year woman presented with a Major Depressive Episode. She was a non-smoker. She had no medical problems. She was on lithium, amitriptyline and sulpiride at the time of commencing sertraline. The amitriptyline was stopped the day the sertraline was commenced. At initial testing her potassium, urea, creatinine, total protein, urates, glucose and thyroid functions were normal and her blood pressure was 140/80. On re-testing her urea was elevated at 7.1 mmol/l. Her blood pressure was unchanged. Her urine and serum sodium and osmolality are presented in the table below (Table 22). No changes were significant.

| | 1st Sample | 2nd Sample – day 14 |
|---|---|---|
| Serum sodium | 139 mmol/l | 141 mmol/l |
| Serum osmolality | 291 mOsm/l | 294 mOsm/l |
| Urine sodium | 98 mmol/l | 34 mmol/l |
| Urine osmolality | 618 mOsm/l | 618 mOsm/l |

**Table 22. Results of subject 6.**

In the table below (Table 23) the statistical analyses are presented confirming that there were no significant differences in the serum and urine sodium concentration and osmolality prior to and during sertraline treatment.

| | P value |
|---|---|
| Serum sodium concentration | 0.24 |
| Serum osmolality | 0.86 |
| Urine sodium concentration | 0.22 |
| Urine osmolality | 0.83 |

**Table 23. P values of comparisons of serum and urine sodium concentration and osmolality prior to and during sertraline treatment.**

# DISCUSSION

## 1.0 Results of first study.

### 1.1 Age, hyponatraemia and SSRIs.

In the data from the Committee on Safety of Medicines, 90% were 60 years and older. This verifies the vulnerability of this population to hyponatraemia. Unfortunately figures of total number of scripts written for SSRIs over this period and the proportion for people over 60 years was not obtained. In their analysis, Liu *et al.* (1996) used 65 years as the cut off age and they found 55.7 % of subjects were older than this. In the report from ADRAC (1996) all 33 cases were over 70 years. They did not specify if they looked specifically at this age group. All these studies suggest a trend that the elderly are most affected.

In the two samples, the Committee on Safety of Medicines sample and the published case report sample, the mean age of the subjects were 77.6 and 78 years respectively. This suggests it is the older elderly most a risk. This is consistent with findings that physiological changes that accompany aging are more marked as age progresses. Particularly the control of AVP secretion in response to osmoreceptors has been noted to be prone to dysregulation after 75 years (Johnson, 1984). Renal changes such as

decreased glomerular filtration rate and renal blood flow are also more likely with greater age.

**1.2 Detection of hyponatraemia.**

The time to detection of hyponatraemia had a large range in the two samples i.e. 1 – 253 days. This is probably because the symptoms associated with hyponatraemia are non-specific and often vague and therefore may be attributed to other reasons. For example, weakness, lethargy, drowsiness, loss of appetite and agitation are all symptoms found in depression. As has been previously noted, hyponatraemia is rarely diagnosed on clinical grounds, particularly in chronic hyponatraemia symptoms are insidious and non-specific (Arieff *et al.*, 1976, Kennedy *et al.*, 1978). The detection of hyponatraemia may therefore be serendipitous when routine blood testing is done or the patient presents with another illness. Obviously when symptoms are severe e.g. confusion, collapse, dyspnoea, then blood testing is more likely to occur. The distribution of the values of the time to detection are skewed to the left with modes of 5 and 7 days. Therefore in the majority of cases blood testing occurred relatively early and hyponatraemia was detected early. A question that has to be answered is how soon after commencing the SSRI does hyponatraemia develop? No cases were reported within 12 hours therefore no cases can be classified as acute. It seems it can occur within days as a lot of cases were detected between days 1 and 7 of treatment. Following on from this, when hyponatraemia occurs and assuming it does occur relatively early in all cases, is it then mild or asymptomatic

when detected much later or conversely can it occur at any time during treatment? It is possible that cases presenting with hyponatraemia after 2 – 3 months of treatment developed another condition or took a drug that altered their physiology facilitating the occurrence of hyponatraemia. Only prospective research will elucidate these questions.

**1.3 Recovery from hyponatraemia.**

An encouraging finding is that in all cases in both samples in which information was given, the serum sodium corrected itself to normal range in 32 days. Of the cases 75% corrected in 16 days. This correction occurred after cessation of the SSRI. As a general impression from the published case reports, many patients did not receive any specific treatment for the hyponatraemia other than cessation of the SSRI and they recovered. When treatment was given it was usually fluid restriction and/or a hypertonic saline infusion.

**1.4 Severity of hyponatraemia.**

A very clear finding from the Committee on Safety of Medicines and published case report samples is that the hyponatraemia, when detected, is moderate to profound. The mean serum sodium concentration in both groups was about 118 mmol/l so half of cases had serum sodium concentrations between 98 and 118 mmol/l. As Arieff et al. (1976)

pointed out, hyponatraemia of this severity is significantly associated with neurological morbidity and mortality. It is not known whether the hyponatraemia associated with SSRIs is predominantly in the moderate to profound range or whether there is a large number of patients receiving SSRIs who develop mild, asymptomatic hyponatraemia that is never detected. If this were the case then the relevance of mild hyponatraemia would have to be determined as it may be insignificant and may not need any action other than monitoring serum sodium levels whilst the patient receives SSRIs. Alternatively if any degree of hyponatraemia heralds the onset of more severe hyponatraemia then detection of mild hyponatraemia may be an important finding that can be acted upon to prevent severe or profound hyponatraemia. Potentially patients at risk could thus be identified. If hyponatraemia does occur early on in treatment then it would be a relatively easy and inexpensive procedure to take a blood sample for analysis of serum sodium and stopping the SSRI if serum sodium is below the normal range. Unfortunately too many questions remain unanswered for such a clinical recommendation to be made.

**1.5 Effect of SSRI on AVP.**

As McAskill & Taylor (1977) hypothesised, since most of these reports of hyponatraemia are of single cases it suggests an idiosyncratic, sporadic occurrence rather than a usual phenomenon with SSRIs. However contrary to this argument is the possibility that there is usually dysregulation of AVP secretion with SSRIs but that this is compensated for by other physiological processes and it is only in patients in whom these physiological

mechanisms are defective that hyponatraemia occurs. This could be tested by prospectively measuring AVP levels in patients starting SSRIs. Unfortunately measuring AVP is an expensive and difficult procedure. In the two cases Girault *et al.* (1997) reported, both subjects had elevated AVP levels in the context of hyponatraemia whilst using an SSRI. What is also not clear is the mechanism by which SSRIs and hyponatraemia are associated. Girault *et al.* (1997) suggest that elevated serum SSRI levels are responsible for increased AVP secretion. With the information that is available this is conjecture and there may be a confounding variable that was responsible for both raised AVP levels and serum SSRI levels. However, looking at other drugs that directly or indirectly affect regulation of AVP secretion, it is more likely that SSRIs have a similar effect.

**1.6 Sex and hyponatraemia.**

The results concur with the finding of other authors that there is a female preponderance. This phenomenon is confirmed by the finding that when the data from the Committee on Safety of Medicines was split into two groups, 60 – 69 years and 70 – 98 years, the female preponderance increased from 61% in the younger group to 76 % in the older group although this was not statistically associated with hyponatraemia. This in part reflects women living longer, therefore representing a greater proportion of the elderly. In developed countries 56% of people aged 65 years are female (Grundy, 1992), and this figure increases with age so that in the over 80 year old age group women comprise up to

70% of that population (Suzman *et al.*, 1992). There is also the increased incidence of depression in women. Prevalence rates for depression in the elderly were reported by Lindesay *et al.* (1989) as 11.3 % in women and 8.4 % in men. It can therefore be postulated that more women would receive SSRI prescriptions. Sex hormones affect AVP secretion in younger women and are probably not a factor in older women (Fraser & Arieff, 1997). It would be interesting to know if hormone replacement therapy had an effect on AVP secretion. None of the reported cases commented on whether or not patients were receiving hormone replacement therapy.

**1.7 Dose of SSRI and hyponatraemia.**

In the published case report and Committee on Safety of Medicines samples, 6.5% and 15% of patients respectively had received dosages of SSRI greater than the minimum starting dose recommended by the pharmaceutical companies. These dosages are fluoxetine 20mg, paroxetine 20mg, sertraline 50mg, fluvoxamine 100mg and citalopram 20mg. Although not recommended by the British National Formulary (British Medical Association and Royal Pharmaceutical Society of Great Britain, 1997), it could be argued that smaller starting doses should be used in the elderly (Newhouse, 1996, Reynolds, 1996). Nevertheless the fact that 85-93.5% cases received a reasonable dose of SSRI nowhere near the maximum dose suggests that developing hyponatraemia whilst using SSRIs is not a dose related adverse reaction. The finding by Girault *et al.* (1997) of elevated SSRI serum levels could be interpreted as there being some abnormality of SSRI

metabolism resulting in elevated serum levels. There is the known subgroups of patients with a deficiency of certain cytochrome P-450 isoenzymes and they may have elevated SSRI plasma levels because these enzymes are necessary for their metabolism (Gram, 1994, Ereshefsky *et al.*, 1996, Nemerof *et al.*, 1996). This subgroup could be at risk of developing hyponatraemia. However if the development of hyponatraemia was related to the serum concentration of SSRI then it would be expected to find higher rates of hyponatraemia in patients receiving larger does of SSRI. This was not apparent in either the Committee on Safety of Medicines or published case report samples. It is also possible that patients on other drugs that are substrates of the cytochrome P450 enzymes that are inhibited by SSRIs are now not efficiently metabolised and they may be the culprits precipitating hyponatraemia. The elderly are physiologically compromised and risk of hyponatraemia may be due the use of multiple drugs and their interaction.

**1.8 Characteristics of hyponatraemia in different age groups and sexes.**

In the re-analysis of the data from the Committee on Safety of Medicines comparing the subjects who were 60 – 69 years with those who were 70 years and older, the most striking finding was that other than the female preponderance being greater in the older group, the two groups were remarkably similar. The same held essentially true when the sample was divided using the mean age as the division point. There were two differences in the latter analysis. Firstly the female to male ratio was slightly lower in the older group, although the female preponderance was well maintained. Secondly the time to

detection of hyponatraemia was significantly shorter in the 79-98 year group. It is possible that the older patients are more likely to be frail and more likely to have other illnesses and thus more likely to be symptomatic. The overall lack of differences found in the different age groups suggests that although the older elderly are at greater risk of developing hyponatraemia, the pathophysiology is the same at whatever age it occurs. The severity of hyponatraemia is also the same when it occurs. The physiological changes making the person vulnerable to developing hyponatraemia occurs at different ages in different people (Rowe, 1992). Presumably the same is true for age related changes in regulation of AVP secretion. Thus the same process can occur at different ages although the frequency is greater with increasing age.

The data was also analysed looking for differences between the sexes in the whole sample. Other than the female to male ratio, no differences were found. There were also no differences found when younger females were compared to younger males and older females to older males using the 60–69 years vs. 70-98 years and 60–78 years vs. 79–98 years groups. This also held true when younger same sex subjects were compared to their older counterparts in these same groups. This also suggests the same pathophysiology occurs in both sexes.

**1.9 Limitations.**

The major bias in the Committee on Safety of Medicines and published case reports samples is that they were comprised of spontaneous reports by clinicians. These reports are thus retrospective, of varying quality and completion. The post marketing surveillance procedure employed by the Committee on Safety of Medicines relies on clinicians identifying adverse reactions to drugs, completing a form and sending it to the agency. It is likely many clinicians do not report adverse reactions and many adverse reactions are never identified. The function of this type of post marketing surveillance is to identify the presence of problems associated with drugs for further research and investigation. It is possible only cases of more severe hyponatraemia were reported and mild cases may not have been considered worth reporting. Because these were spontaneous reports, no estimates of incidence can be inferred from these figures. The information given was often incomplete and certainly symptoms patients presented with were poorly reported. However when repeated reports are received of an adverse reaction associated temporally with a particular drug a causal relationship can be strongly suspected. This causal relationship can then strictly only be verified once a pathophysiological mechanism is identified and tested. Most accepted adverse drug reactions of most drugs are identified only through being regularly reported in association with use of the particular agent. The acceptance of hyponatraemia as an adverse reaction to SSRIs has been by these same standards that are not scientifically rigorous.

Case reports were pooled and then analysed because they were all presented in similar format so the information gleaned from each report was comparable. Most reports were of single cases. A meta-analysis would not have been appropriate.

**2.0 Results of second study.**

Looking at the second study, some questions can be answered. Firstly, none of the six subjects showed any alteration in serum and urine sodium concentration and osmolality that would suggest dysregulation of AVP secretion. This immediately answers the question that hyponatraemia is most likely not a usual phenomenon during the first 2 – 3 weeks of treatment with an SSRI. This can only be definitively answered by measuring AVP directly. The most important contribution to plasma osmolality is made by sodium and then in descending order of importance urea, glucose and protein (Hodgkinson, 1977). In all six subjects their sodium and total protein concentrations were normal. All six subjects had at least one raised urea concentration and three had elevated glucose concentrations. The abnormal urea and glucose concentrations were compensated for because serum osmolality remained within normal limits.

The ages of the six subjects ranged from 76 years to 83 years, which put them in the age group most frequently reported to develop hyponatraemia with SSRI use. None of the subjects had a current medical illness commonly associated with SIADH, although two had a background history of breast carcinoma and one of these had a background history

of tuberculosis. Prior to starting sertraline all six subjects were on drugs known to be associated with SIADH. The relevant drugs were non-steroidal anti-inflammatory drugs, , diuretics, antipsychotics, lithium and nicotine (smoking). Five subjects were also taking drugs that are metabolised by the five Cytochrome P450 isoenzymes relevant to SSRIs namely non-steroidal anti-inflammatory drugs, tricyclic antidepressants, benzodiazepines and antipsychotics. Only CYP 2D6 is known to be significantly inhibited by setraline so of the drugs taken only thioridazine posed a known risk of interaction by this mechanism. The sixth subject was taking digoxin, which is highly protein bound, and may have been displaced by Sertraline, which is also highly protein bound.

All six subjects had a depressive illness which may be associated with altered regulation of AVP secretion. So despite these significant factors being present that could have made them vulnerable to developing hyponatraemia, none of them did. This could lead to the hypothesis that the number of conditions or drugs associated with SIADH present in any one patient do not increase the risk of developing SIADH in a cumulative manner, but rather that each illness or drug is a risk factor independent of each other. Unfortunately this assumption cannot be tested in such a small sample. However if this hypothesis were true then it would not be helpful to identify illnesses and drugs associated with SIADH as a way of predicting if a patient would develop hyponatraemia when commencing an SSRI, although obviously these factors increase the overall likelihood of the patient developing hyponatraemia.

**2.1 AVP secretion in presence of SSRIs.**

It is interesting to note the serum osmolality in all six cases was above the threshold for AVP secretion (280 mmol/l), serum sodium concentration was normal and the urine was concentrated. From this it can be inferred that AVP is being secreted appropriately and water balance is maintained. These subjects are probably slightly in negative water balance suggested by serum osmolality in the higher range of normal and concentrated urine and this is probably because of the blunted thirst response associated with aging. An interesting intervention would be to give them a fluid challenge and see if water balance is maintained or if they develop hypo-osmolar hyponatraemia because of persistent AVP secretion i.e. are they being 'saved' by their blunted thirst response?

**2.2 Limitations**

A major shortcoming of this part of the study is that serum AVP levels were not directly measured. The sample size is small making generalisations invalid. There was also no control group, but this would have been difficult to set up as so many variables would have had to have been matched e.g. age, sex, illnesses, drugs etc. Taking the blood sample between two to three weeks may have missed any alterations in AVP function immediately on starting sertraline which may subsequently have been corrected. If hyponatraemia had occurred the only evidence suggesting a causal relationship with sertraline would have been time, nevertheless this would not have excluded the

hyponatraemia being due to another drug, illness or an idiopathic reaction. This distinction would be difficult to make even if AVP levels were measured. From the point of view of confounding variables the sample was typical of patients presenting to psychogeriatric services.

## 3.0 Null Hypothesis

The data from the published case reports and the Committee on Safety of Medicines suggest the null hypothesis may be false however the results from the six subjects taking sertraline upheld the null hypothesis. It is reasonable to infer the null hypothesis is sometimes false.

## 4.0 Conclusions

In summary there is an association between SSRIs and hyponatraemia. It is probably is a sporadic, idiosyncratic phenomenon that is not dose related. The exact mechanism is not known although there have been two cases reported with elevated AVP levels and in reported cases in the literature urine and blood pictures have been compatible with SIADH. The elderly are at greater risk and the older elderly, over 70 years, are at greatest risk. Females comprise the majority of the cases but this has more to do with factors such as longevity and incidence of depression than women being at greater risk. The

physiological characteristics of the hyponatraemia is similar at whatever age it occurs and in both sexes.

It is very likely that the hyponatraemia occurs within the first two weeks of treatment so clinicians should look for it if patients present with non-specific symptoms, even if these symptoms could be explained by other conditions present, including depression. Most cases of hyponatraemia resolve within about two weeks of stopping the SSRI. The cases of hyponatraemia reported thus far were predominantly moderate to profound so it should be taken seriously as hyponatraemia of this severity is associated with considerable morbidity and mortality.

There are further questions that still need clarification. It is not known whether inappropriate secretion of AVP is sufficient to cause hyponatraemia or if hyponatraemia only occurs when there is another defect in physiological mechanisms maintaining water balance, such as those occurring in the elderly. Polypharmacy and drug interactions particularly involving the cytochrome P450 enzymes may also play a role. It is also unclear if the hyponatraemia is generally moderate to profound or if there is a large group of patients developing mild hyponatraemia that is never detected or reported. It would be helpful to be able to predict who would be at risk of developing hyponatraemia prior to starting the SSRI. Thus far the only clear predictor is age. The presence of other illnesses or drugs associated with SIADH or physiological changes affecting control of water balance need to be further investigated to establish their predictive value.

This study of six prospective cases merely gives an indication of the effects of an SSRI and clinical recommendations cannot be made from such a small sample. More prospective studies over longer periods of time are needed directly measuring AVP in people using SSRIs to establish if hyponatraemia is related to serum SSRI levels and inappropriate secretion of AVP and how this relates to compromised physiology and drug interactions.

## 5.0 Clinical Recommendations

From this investigation it can be recommended to clinicians that it is advisable to test serum sodium concentration within the first two weeks of starting an SSRI in the elderly. Hyponatraemia should be considered in patients who present with non-specific symptoms such as confusion, weakness, lethargy ,drowsiness. If hyponatraemia occurs the SSRI should be stopped and serum sodium concentration monitored until it returns to normal, usually within 2-3 weeks. If serum sodium concentration does not begin improving within in the first few days of stopping the SSRI other causes of hyponatraemia must be considered. The patient could be rechallenged with a different SSRI whilst serum sodium concentration is carefully monitored.

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