

ANTIDEPRESSANTS AND HYPONATREMIA IN A PATIENT WITH COLECTOMY – A CASE REPORT

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SUMMARY

Antidepressants are routinely used by General Practitioners (GP) as well as Psychiatrists to treat Depression. They are tolerated well. However, in certain patient populations, they are associated with SIADH (Syndrome of Inappropriate Anti-Diuretic Hormone Secretion) and Hyponatremia. Various research studies have shown that all antidepressants are associated with Hyponatremia. Hyponatremia as a side effect of antidepressant therapy is more commonly seen in old age, chronic Kidney disease and Hypothyroidism. Untreated Hyponatremia could lead to life threatening emergencies including Cerebral oedema, brain damage and coma.

In this article, the authors discuss a 63 year old patient who suffered from Bipolar Disorder Type 2. He was treated with antidepressants (mainly Paroxetine) on and off for 30 years, without much side effects, until 2014. In July 2012, he underwent subtotal colectomy with ileorectal anastomosis as a management of adenocarcinoma of Colon. In April 2013, Paroxetine was stopped as he was well. He developed first episode of mania in July 2014. This was managed with Olanzapine. However, he soon developed a Depressive episode and severe Anxiety. He was restarted on Paroxetine and the dose was increased up to 50 mg along with Olanzapine 15 mg per day. As he did not improve, he was switched to Sertraline with which he developed Hyponatremia. Further to this, he was tried on Venlafaxine and Lofepramine and he developed Hyponatremia with both of them. Considering the severity of Depression, he was started on Mirtazapine and the dose was titrated to 45 mg. With this dose his serum Sodium levels were stable but his Depression persisted. Fluoxetine augmentation at this stage by the GP led to another episode of Hyponatremia. Hence, he was started on Aripiprazole 5 mg as an augmentation agent. His Depression improved reasonably (though he did not remit fully). Recently, he has been started on Vortioxetine and the dose has been titrated to 15 mg OD and in addition, he is on Mirtazapine 45 mg OD and Aripiprazole 5 mg OD. His Sodium levels have been stable and his Depression has improved. This is the first time we have come across a patient with colectomy developing severe Hyponatremia. In this article, we have discussed possible reasons for Hyponatremia following colectomy and the management strategies that could help.

Key words: Hyponatremia – depression - antidepressants

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INTRODUCTION

Epidemiological show an increase in the lifetime prevalence of Depression. This ranges from 2.9% to 19% in different countries. Untreated Depression could not only lead to loss of life by suicide but also disability leading to financial and social difficulties. Therefore, Depression needs to be treated with appropriate biopsychosocial approaches. In most circumstances, depressed patients are initially seen by the General Practitioner (GP) in primary care and are started on medication and the usual first lines of antidepressants are Selective Serotonin Reuptake Inhibitors (SSRI). These are generally highly effective and tolerated well. When a patient does not respond to SSRI, other antidepressants are tried by the GP in primary care or Psychiatrist in secondary care. There are specific guidelines on initiating and maintain antidepressants as well as augmentation strategies (Cleare 2008, NICE. 2017). In routine clinical practice, patients are briefed about and reviewed regularly with regards to common side effects related to sleep, SIADH and sexual difficulties etc.

Occasionally, in certain populations or high risk patients, they may experience other side effects which could be life threatening. One such side effect is Hypo-

natremia. Hyponatremia is a condition that occurs when the level of Sodium in the blood is abnormally low. Sodium helps regulate the amount of water that's in and around the cells. It helps maintain normal blood pressure, supports the work of the nerves and muscles, and regulates the body's fluid balance. A normal Sodium level is between 135 and 145 milliequivalents per litre (mEq/L) of sodium. Hyponatremia occurs when the Sodium in the blood falls below 135 mEq/L. Various research studies have shown that all antidepressants are associated with Hyponatremia. Hyponatremia as a side effect of Antidepressant therapy is more commonly seen in common in old age (Gandhi 2017, Manisha Sahay 2014), chronic Kidney disease and Hypothyroidism. Untreated Hyponatremia could lead to nausea and vomiting, headache, confusion, loss of energy and fatigue, restlessness and irritability, muscle weakness, spasms and cramps all the way to life threatening emergencies including seizures, Cerebral oedema, brain damage, coma and death (UKMi 2017, Manisha Sahay 2014). Premenopausal women appear to be at the greatest risk of hyponatremia-related brain damage. This may be related to the effect of women's sex hormones on the body's ability to balance sodium levels.

Table 1. Timeline of Medication

Date	Mood episode	Medication used
Until April 2013	Recurrent Depressive episodes	Paroxetine upto 50 mg OD
July 2013	First episode of Mania	Olanzapine 5 mg nocte
November 2013 - June 2014	Depressed and Anxious	Olanzapine 10 nocte Paroxetine restarted & titrated 50 mg OD
July 2014 and August 2014	Depressed and Anxious	Olanzapine 10 mg nocte and Sertraline up to 200 mg OD
September 2014	Depressed and Anxious	Olanzapine 10 mg nocte and Venlafaxine up to 75 mg twice a day.
October 2014	Depressed and Anxious	Olanzapine 7.5 nocte Pregabalin started
November 2014	Depressed and Anxious	Olanzapine stopped Lofepramine 70 mg Od started and stopped Pregabalin continued Diazepam 5 mg PRN Oral for anxiety
January and February 2015	Depressed and Anxious	Quetiapine 100 BD Pregabalin 150 TDS Diazepam 5 mg OD
March 2015 - June 2015	Depressed and Anxious	Quetiapine 100 BD Pregabalin 150 TDS Diazepam 5 mg OD Mirtazapine added & titrated 30 mg nocte
June 2015	Depressed and Anxious	Quetiapine 100 BD stopped Mirtazapine 30 mg nocte Pregabalin 150 TDS Diazepam 5 mg OD
September 2015	Depressed and Anxious	Fluoxetine started and stopped Continued Mirtazapine 30 mg nocte Pregabalin 150 TDS Diazepam 5 mg OD
November 2015	Depressed and Anxious	Lamotrigine started and stopped Continued Mirtazapine 30 mg nocte Pregabalin 150 TDS Diazepam 5 mg OD
January 2016 - March 2017	Depressed and Anxious	Pregabalin 150 TDS gradually stopped by the patient himself Diazepam 5 mg OD stopped by the patient himself (improvement in Anxiety)
April 2017- August 2017	Depressed	Vortioxetine 5 mg OD started & titrated to 15 mg OD Mirtazapine 45 mg nocte
Current Medication		Aripiprazole 5 mg OD

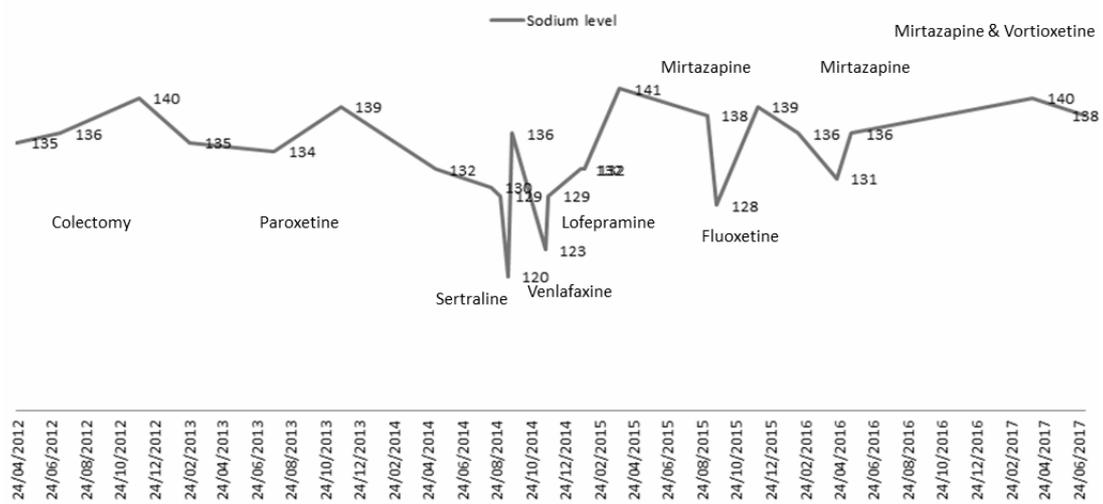


Figure 1. Graph of Sodium levels and Antidepressants used

This is the first time we have come across a patient with Colectomy developing severe Hyponatremia. In this article, we have discussed possible reasons for Hyponatremia following Colectomy and the treatment management strategies that could help

RISK FACTORS FOR DEVELOPING HYPONATREMIA

Age

Older adults may have more contributing factors for Hyponatremia, including age-related changes, taking certain medications and a greater likelihood of developing a chronic disease that alters the body's Sodium balance.

Certain drugs

Medications that increase the risk of Hyponatremia include thiazide diuretics as well as some antidepressants (Leth-Møller 2016) and pain medications.

Ecstasy

This amphetamine increases the risk of severe and even fatal cases of Hyponatremia.

Conditions that decrease the body's water excretion

Medical conditions that may increase the risk of Hyponatremia include Kidney disease, syndrome of inappropriate anti-diuretic hormone (SIADH), Heart failure and certain diseases affecting the Liver can cause fluids to accumulate in the body, which dilutes the Sodium in the body, lowering the overall level.

Hormonal changes

Addison's Disease affects the Adrenal glands' ability to produce hormones that help maintain the body's balance of Sodium, Potassium and water. Low levels of Thyroid hormone also can cause a low blood Sodium level.

Intensive physical activities

People who drink too much water while taking part in marathons, ultramarathons, triathlons and other long-distance, high-intensity activities are at an increased risk of Hyponatremia.

Chronic, severe vomiting or diarrhoea

This causes the body to lose fluids and electrolytes.

Dehydration

Taking in too little fluid can be a problem and the body loses fluids and electrolytes.

CASE DETAILS

A 63 year old patient had Depressive episodes on and off in his life for the past 30 years. He was treated with antidepressants (mainly Paroxetine) on and off for 30 years, without much side effects; until 2014. He had one severe Depressive episode in his 30s which needed inpatient hospitalisation. Other than this, he had mild to

moderate Depressive episodes which were mainly treated by the GP in the community. He had a stable family life and from a premorbid perspective, he was a stable outgoing person who was highly motivated and willing to face challenges. He smoked cigarettes but stopped them in 2014. He had always been a drinker of alcohol and used to drink 4-10 cans of lager in the evenings. He suffered from Hypertension and was treated with Felodipine 10 mg OD and Candesartan 15 mg nocte.

In July 2012, he underwent subtotal Colectomy with ileorectal anastomosis as a management of Adenocarcinoma of Colon. In April 2013, Paroxetine was stopped as he was doing well. He developed his first episode of Mania in July 2013 and the diagnosis was changed to Bipolar Disorder Type 2. He was started on Olanzapine and was titrated up to 15 mg at bedtime. However in November 2013, he developed a Depressive episode with severe Anxiety. His depressive symptoms included low mood, lack of energy, amotivation and procrastination. His cognitive functions were intact with an MMSE (Mini Mental State Examination) score of 30/30 and intact clock drawing.

He was restarted on Paroxetine and the dose was titrated up to 50 mg along with Olanzapine 15 mg per day. As he did not improve with this, he was switched to Sertraline with which he developed Hyponatremia. Therefore, he was tried on Venlafaxine and Lofepamine and he developed Hyponatremia with both of them. Considering the severity of Depression, he was started on Mirtazapine and the dose was titrated to 45 mg. With this dose, his serum Sodium levels were stable but his Depression persisted. Fluoxetine augmentation (Mohamed 2017) at this stage by the GP led to another episode of Hyponatremia. Hence, he was started on Aripiprazole 5 mg as an augmentation agent. His Depression improved reasonably (though he did not remit fully). Recently, he has been started on Vortioxetine and the dose has been titrated to 15 mg OD. In addition, he is on Mirtazapine 45 mg OD and Aripiprazole 5 mg OD. His Sodium levels have been stable and his Depression has improved (Table 1, Figure 1).

Over a period of time, he was investigated comprehensively including Thyroid function tests, Liver function tests, Renal functions, Serum B12, Folic Acid levels as well as Carcinoembryonic Antigen (CEA) which were all within normal limits. Gamma GT (GGT) was only slightly raised. In May 2017, he had a MRI Brain scan which was normal.

DISCUSSION

Analysis of this patient's case history taught us the following lessons. This patient had a Subtotal Colectomy in July 2012. Colon is the main site for resorption of water and sodium. Hence, the removal of the Colon should result in water and Sodium loss in the stools. However, resection of Colon and Ileo-Rectal pouch

anastomosis causes water and Sodium absorption from the pouch. Also, Kidneys absorb more Sodium and water to compensate the water loss. We searched PubMed and Google scholar to get relevant literature on similar cases, i.e. Antidepressant use and Hyponatremia in patients with Colectomy. We could not find any literature. Our hypothesis was that this patient was in a compensated state of Sodium homeostasis following Colectomy. However, use of Antidepressant and SIADH could have disturbed this homeostasis, preventing renal resorption of Sodium.

Interestingly, when this patient had a relapse of Depression in 2014, he was treated with Paroxetine for more than six months without Hyponatremia. As Paroxetine was ineffective, he was switched over to Sertraline and he then developed Hyponatremia. He was subsequently tried on Venlafaxine and Lofepramine which again resulted in Hyponatremia. Treatment with Mirtazapine, Vortioxetine and a combination of both did not lead to Hyponatremia. On the other hand, when this patient was given Fluoxetine with Mirtazapine he developed Hyponatremia. Hence, we went through any other confounding factors which could have caused Hyponatremia.

One factor that could have caused Hyponatremia in this patient is Colon Cancer causing Paraneoplastic syndrome of inappropriate secretion of ADH. However, this patient's annual check showed normal Carcinoembryonic Antigen (CEA) for the past 5 years. Also, the specialist assessment did not show any relapse.

This patient has been drinking alcohol at increased levels for a long time. However, all along, his Liver functions were within normal limits except for slightly raised Gamma GT.

Finally, we wondered whether concomitant medication i.e. Antipsychotics (Olanzapine, Quetiapine or Aripiprazole) or Pregabalin could be associated with SIADH or Hyponatremia. Interestingly, there were periods when he was only on Olanzapine or Pregabalin. There was also another occasion when he was on Pregabalin and Quetiapine. On these occasions, his Sodium levels were within normal limits. When Aripiprazole was started, this patient started showing an improvement in Depressive symptoms. Also, his Sodium levels remained stable. He has shown an improvement in his Anxiety and Depressive symptoms when Aripiprazole was used at a very low dose to augment Mirtazapine. With the emergence of evidence for Aripiprazole in the treatment of Depressive symptoms, this case also strengthens the idea that in patients who are prone for Hyponatremia with Antidepressants, a low dose of Aripiprazole could be used to treat Depression. Also Mirtazapine and Vortioxetine were safely used to treat his Depression without causing Hyponatremia.

CONCLUSION

Antidepressant medication is associated with Hyponatremia (Cury 2006). Hyponatremia induced by Antidepressants can occur anywhere between 1 day and

several months after initiation of treatment (Movig 2002). The mechanism by which SSRIs lower serum Sodium is unknown. New onset of gastrointestinal symptoms or cognitive impairment should prompt an urgent sampling of serum sodium.

The usual risk factors considered are old age, Heart dysfunction and renal pathology in addition others as described above. Antidepressants should be cautiously used in patients who have undergone Colectomy. Clinicians must be aware of this adverse effect, particularly in the elderly and in patients taking concomitant diuretics.

In this case, a low dose of Aripiprazole, Mirtazapine and Vortioxetine were safely used to treat Depression in the patient who had undergone Colectomy.

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Madhavan Seshadri: compiling the case report, analysis, literature review and writing the article;

Madhusudan Deepak Thalitaya: literature review and writing the article;

Tuno Simon: literature review and writing the article;

Catherine Odelola: literature review and writing the article;

Humphrey Enow: literature review and writing the article.

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