CASE REPORT

# Possible SAMe-induced mania

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## SUMMARY

This paper describes a patient who presented with mania with psychotic features in the context of concomitant use of S-adenosyl-L-methionine (SAMe) and selective serotonin reuptake inhibitor (SSRI). The aim of this case report is to provide medical practitioners with a greater awareness of the possibility of a psychotic episode and/or mania manifesting with concurrent use of SAMe and SSRI.

## BACKGROUND

There are very limited reports on S-adenosyl-L-methionine (SAMe) induced mania. As stated, it is important for medical practitioners to be aware of the possibility of mania and/or psychosis manifesting with concurrent use of SAMe with selective serotonin reuptake inhibitor (SSRI).

## CASE PRESENTATION

This is the case of a 37-year-old single woman, currently residing alone in her rental unit and employed as an administrative officer. Eight months prior to hospitalisation, she began to use SAMe in conjunction with an SSRI (namely, escitalopram 10 mg mane) to 'try nutrient therapy instead of medication to get better'. According to the patient, the SSRI was commenced by her general practitioner (GP) for depression 7 months prior to the commencement of SAMe. The combination of treatment was monitored by her GP. The patient reported tobacco use four times a day and denied illicit substance use. According to the patient, she consumed 1–2 standard drinks a few times a year, and she denied any past bingeing patterns of alcohol consumption. There was no history of alcohol use disorder. On the day of the incident, she reported being distressed by the hallucinations and had several alcoholic drinks in an attempt to calm down. Her medical history consisted of chronic fatigue syndrome and polycystic ovarian syndrome. She recalled her mother and sister having 'mood swings' but neither of them is known to have received a formal diagnosis nor received any form of treatment for the same.

On the day of the incident, the patient was brought into the emergency department by ambulance after a self-initiated call with a history of worsening of auditory hallucinations, seeing things and feelings of being persecuted following an alcohol binging episode. On arrival to the hospital, she had a blood alcohol level of 0.144%. The patient reported experiencing mild persecutory delusions 1–2 weeks after being on the combination of SSRI and SAMe. She stated the persecutory delusions worsened over a period of time. The content of the persecutory delusions included being followed and spied on while attending her local fitness centre. She also believed that federal police were watching her, her Facebook and internet had been hacked and she was involved with the Bali nine bombings. On the day of the admission, she reported seeing and talking to a cat in her lounge room when she did not own a cat. She reported labile mood, racing thoughts, decreased need for sleep and increased energy levels. She denied any history of risk-taking behaviours, increased goal directed activity or psychomotor agitation. She denied having grandiose delusions, passivity phenomena or thought alienation. The patient denied suicidal ideation at the time of admission to the hospital.

## INVESTIGATIONS

On admission, the patient's urine drug screen was negative and routine blood investigations, including thyroid function tests revealed no abnormalities. CT scan of the brain was normal.

The patient had a blood alcohol level of 0.144% on presentation to the hospital. However, her gamma-glutamyl transferase level was within normal range, and other liver function test results were normal confirming there was no alcohol use disorder.

## DIFFERENTIAL DIAGNOSIS

On admission, delirium was considered as an initial differential diagnosis. However, this was excluded as she was well oriented, the trail making test was normal and the thorough medical workup and investigations did not reveal any abnormalities.

Mood disorder/psychotic disorder secondary to medical conditions were also considered as a differential diagnosis on initial presentation. These were excluded following thorough medical workup and investigations.

On admission, illicit substance-induced mood disorder or psychotic episode was excluded as there was no history of illicit substance use, and the urinary drug screen was normal.

Serotonin syndrome was also considered as a possible differential diagnosis on admission, however as there was no history of confusion, headaches, sweating, autonomic instability and myoclonus, this was soon excluded.

A differential diagnosis of SSRI-induced mania was also considered. However, this was excluded, as the symptoms of persecutory delusions with mania started with the introduction of SAMe to the existing SSRI treatment without any dose



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adjustment to SSRI (SSRI was commenced 8 months prior to the commencement of SAMe).

Therefore, the diagnosis was updated to substance/medication-induced mood disorder.

## TREATMENT

At the time of admission, the patient had poor insight into her mental illness, the need for treatment and lacked capacity to consent for treatment. She was, therefore, placed under the mental health act during the admission. She was commenced on oral aripiprazole 10 mg mane on admission, and escitalopram and SAMe were ceased. Her mental state was stabilised within a week with reduction of symptoms. Four-weekly depot injection aripiprazole 400 mg was commenced prior to discharge from the ward as the inpatient treating team was concerned regarding the possibility of her poor compliance due to her ongoing poor insight into her presentation to the hospital. There was no definitive diagnosis on discharge, and a differential diagnosis of bipolar affective disorder type 1 versus brief psychotic disorder was given. The patient was referred to the community mental health team for case management and follow-up. During the longitudinal assessment, it was confirmed that symptoms of persecutory delusions with mania started with the commencement of SAMe, followed by deterioration in mental state resulting in mental health admission. Engagement and psychoeducation along with ongoing treatment helped the patient to gradually develop insight into her mental illness and what precipitated her hospital admission. In light of these improvements, she was made voluntary. The patient remained stable in mental state with no symptoms; hence, depot aripiprazole was ceased after 3 months. She was followed up for a further 3 months to monitor for re-emergence of symptoms without psychotropic medications. Having maintained stability throughout this period, she was discharged to her GP's care.

### Total duration of treatment

The patient was treated in the inpatient unit for 1 week and then discharged to the community mental health service (outpatient) where she received monthly depot aripiprazole 400 mg for a total of 3 months. She was further followed up via the community mental health service for 3 months to monitor for re-emergence of symptoms without psychotropic medications. The patient was case managed as an outpatient for a total duration of 6 months as per the local community mental health protocols prior to discharge back to her GP.

## OUTCOME AND FOLLOW-UP

Engagement and psychoeducation along with ongoing treatment helped the patient to gradually develop insight into her mental illness and her hospital admission. In light of these improvements, she was made voluntary. The patient remained stable in mental state with no symptoms; hence, depot aripiprazole was ceased after 3 months. She was followed up for a further 3 months following cessation of psychotropic medications to monitor for re-emergence of symptoms. Having maintained stability throughout this period, she was discharged to her GP's care.

On discharge to GP care, advice was provided both to the patient and the GP in monitoring for early warning symptoms and signs for the next 6 months. Advice was also offered encouraging close monitoring of her mental state, should the need arise for future prescription of hormonal, steroid or stimulant medications.

## DISCUSSION

SAMe is a natural substance found in all human cells which is formed by a reaction between an essential amino acid, methionine, and ATP.[1] As a physiological donor of the methyl group, it is involved in cellular functions in the metabolism and synthesis of neurotransmitters such as catecholamines, membrane phospholipids, fatty acids, nucleic acids, porphyrins, choline carnitine and creatinine. SAMe is proficient at crossing the blood–brain barrier, and this ability has led to immense research regarding its function as a neurological agent.[2] Aside from being trialled to treat depression, it is widely studied for its potential role in osteoarthritis and fibromyalgia.[3–6]

Possible adverse effects of SAMe, in particular mania, were assessed in both patients with a history of bipolar disorder and in those with no suggestion of bipolar disorder.[7–9] Carney *et al* observed that 9 of 11 patients with bipolar disorder exhibited a switch to elevated symptoms consistent with hypomania, mania or euphoria. Goren *et al* reported that SAMe caused a transient mixed manic episode with suicidal ideation in an individual with no previous psychiatric history. The discontinuation of SAMe resulted in recovery to baseline for this individual.[10]

A 2016 Cochrane review involving randomised controlled trials evaluated participants from age 18 to 70 years with a diagnosis of major depression with or without psychotic symptoms according to the Diagnostic and Statistical Manual of Mental Disorders IV or International Classification of Diseases 10. Participants with bipolar depression and schizoaffective disorder were excluded. Eight trials comparing SAMe with either placebo, imipramine, desipramine or escitalopram were evaluated. Trials where SAMe was used as monotherapy or as add-on therapy to a SSRI were included. The review encompassed 934 adults and reported no evidence of a difference in terms of change to depressive symptoms with the use of SAMe as a monotherapy. It revealed little evidence that SAMe is superior to placebo, as an add-on to SSRIs in terms of exhibiting a change in depressive symptoms from baseline. It was concluded that SAMe demonstrated no difference compared with placebo or approved antidepressants, yet it did demonstrate low-quality efficacy in some patients.[2]

A double-blind, randomised, placebo-controlled clinical trial by Mischoulon *et al* on SAMe versus escitalopram in major depressive disorder failed to support an advantage over placebo for either the investigational treatment SAMe or the standard treatment escitalopram.[11]

Contrary to the results of the Cochrane review, meta-analyses of randomised controlled trials evaluating SAMe and its role in depression revealed a superior efficacy compared with placebo, with efficacy equivalent to tricyclic antidepressants.[12–14] A parallel study by Crellin *et al* that included more than 1400 patients with major depressive disorder demonstrated that SAMe was as effective as a placebo in 13 trials, and as effective as a tricyclic antidepressant in 19 trials.[15]

The open trial study by Jonathan *et al* showed that SAMe can be used as an adjunct for resistant major depressive disorder following partial response or non-responsive to SSRIs or venlafaxine.[16] In a study done by George *et al*, the preliminary results suggested that SAMe can be an effective, well-tolerated and safe adjunctive treatment strategy for SSRI non-responders with major depressive disorder.[17]

## Learning points

- ► There is no conclusive evidence that S-adenosyl-L-methionine (SAMe) is an effective monotherapy for major depressive disorder. It may be possible that it exerts partial efficacy in the treatment of mild depression.
- ► It is vital, to acknowledge the limitations of these studies, as sample size was extremely small and largely excluded patients with a family history or diagnosis of bipolar disorder. Therefore, there is a need for more robust evidence before prescribing SAMe as a treatment for major depression.
- ► Clinicians need to be cautious when considering prescribing SAMe in combination with serotonergic agents.
- ► In this patient's case, it is possible that she had a genetic vulnerability to development of a bipolar disorder which was unmasked with the concomitant use of SAMe and a selective serotonin reuptake inhibitor. This is further supported by the suggestion that her mother and sister suffered from 'mood swings' as per the history.
- ► It is important for clinicians to be aware of the risk of patients switching to hypomania or mania while on a combination of an antidepressant and SAMe. It is also important to take a thorough history when assessing patients to exclude undiagnosed hypomania or a family history of mood disorder.

**Contributors** This work was carried out in collaboration between both authors. HA is the consultant psychiatrist who treated the patient at the community mental health service. He designed the case report and helped in writing the report. RG is a medical student who was attached to the community mental health service during her placement. She researched for evidence for and against SAMe and helped in writing the case. Both authors read and approved the final manuscript.

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