Resolution of antipsychotic-induced amenorrhea using aripiprazole

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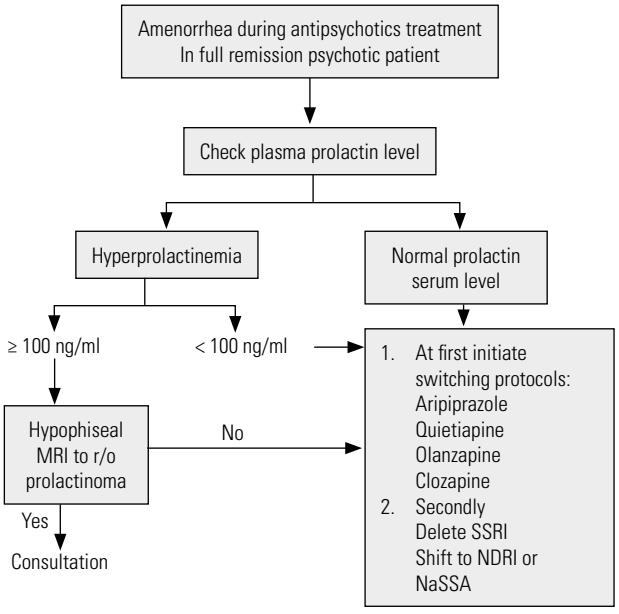
Dear Editor,

Antipsychotic-induced[1] amenorrhea is a serious concern among premenopausal women suffering from mental disorders. Among many women, menstruation is a symbol of femininity that indicates the ability to become pregnant naturally, or is a basis to determine if they are menopausal[2]. Some patients believe the lack of menstruation signifies menopause and contributes to emotional instability or aggravation of their mental disorder. Patients with amenorrhea often seek help from gynecologists to induce menstruation. Peuskens *et al.*[3] reported that amenorrhea occurred in 22-50% of women treated with antipsychotics. The prevalence of menstrual irregularities and amenorrhea is considered to be 15-97% in women receiving therapy for a psychotic disorder[4]. It is also common for patients to discontinue antipsychotics due to amenorrhea, which in turn triggers relapses.

I will discuss two cases here: a patient with schizoaffective disorder and another with bipolar I, manic episodes with psychotic features. Both patients achieved full remission of psychotic symptoms, but wanted to switch medications due to lack of menstruation and weight gain. Both patients were middle-aged women in their 40s, with multiple past records of discontinuing their medication that triggered relapses and led to hospitalization. Therefore, I prescribed aripiprazole to facilitate a gradual process of switching medications. Table 1 summarizes the history of past medications, medication switching process, and results of therapy for the two patients. Notably, amenorrhea does not only occur among patients with hyperprolactinemia, but also among premenopausal patients with normal blood prolactin levels, even when using multi-acting receptor targeted antipsychotics (MARTAs), which have an extremely low probability of causing amenorrhea.

Among antipsychotics, hyperprolactinemia is most commonly induced by sulpiride, amisulpride, risperidone, and paliperidone. Paparrigopoulos *et al.* found that the prevalence rate of hyperprolactinemia induced by amisulpride was 100%, and this was observed more in women than in men[5]. The prevalence of menstrual side effects such as amenorrhea in patients on risperidone is reported to be 1-10%[6]. In addition, serotonin-dopamine antagonists (SDAs) are more likely to induce hyperprolactinemia than MARTAs. Psychiatrists thus often use MARTAs, such as olanzapine and clozapine[1], to treat female psychotic patients with amenorrhea. However, it has been reported that even olanzapine may lead to hyperprolactinemia[7].

Aripiprazole is regarded as a second- or third-generation antipsychotic, mainly because it provides a control mechanism for the dopamine "see-saw". It reduces the dopaminergic neuron activity in brain regions with dopamine hyperactivity, while increasing the dopaminergic neuron activity in regions with hypoactivity, thereby reducing the number of side effects; regarding reduced side effects, the resolution of hyperprolactinemia has attracted the most attention. Aripiprazole can be used to resolve hyperprolactinemia induced by risperidone[8], amisulpride, and ziprasidone[9]. However, the use of aripiprazole to resolve MARTA-induced amenorrhea has rarely been reported, especially in amenorrhea without hyperprolactinemia. Some may believe that since aripiprazole can reduce amenorrhea, we should attempt to use it in the early stages of disease onset in women. It should be noted that in Case 2, aripiprazole was used during the early stages of disease onset. However, due to its slow antimanic effect, it was combined with zotepine after four weeks, and was only completely replaced by zotepine (100 mg/d) after eight weeks, followed by a switch to aripiprazole after the unexpected occurrence of amenorrhea. In both cases, full D2 antagonists were used initially for rapid therapeutic effect until full remission of the mental disorder, and then were successfully replaced by aripiprazole completely over one to two months. This was a viable therapeutic strategy.



SSRI: selective serotonin reuptake inhibitors; NDRI: norepinephrine-dopamine reuptake inhibitor; NaSSA: noradrenergic and specific serotonergic antidepressants.

Figure 1. Summary of the clinical algorithm used patients are suspected of antipsychotic-induced amenorrhea[7].

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Table 1. Summary of past medications, medication switching process, and results of therapy for the two patients

	Patient 1	**Patient 2**
Diagnosis	Schizoaffective disorder	Bipolar I, manic episode with psychotic features
Age	44	43
Past medications	2011 Risperidone 2 mg/d 2013/1 Zotepine 100 mg/d 2013/8 Olanzapine 10 mg/d + sertraline 50 mg/d (body weight increased 20 kg) 2014/9 Risperidone 3 mg/d 2014/12 Began to visit gynecologist every month till 2015.10.14 2015.9.16 Last prescription at gynecology out-patient department Above are the past discharge medications, out-patient medications and gynecological follow-up visits	2009 Lithium 900 mg/d+ Valproic acid 900 mg/d+ Risperidone 4 mg/d 2010/3 Lithium 600 mg/d+ Valproic acid 1000 mg/d+ Risperidone 3 mg/d 2010/7 Valproic acid 750 mg/d+ Risperidone 3 mg/d 2013 Valproic acid 500 mg/d+ Risperidone 3 mg/d 2014 Lithium 600 mg/d + Risperidone 3 mg/d Above is the past discharge medication list. Below are the medications prescribed during this hospitalization 2016/5/13 Aripiprazole 30 mg/d 2016/5/25 Aripiprazole 30 mg/d Dogmatyl 200 mg/d 2016/6/8 Aripiprazole 30 mg/d Zotepine 50 mg/d 2016/7/4 Zotepine 75 mg/d+ Lithium 900 mg/d 2016/7/5 Zotepine 100 mg/d+ Lithium 900/d 2016/7/13 Zotepine 100 mg/d+ Lithium 600 mg/d
Medication switching process	2015.8.19 LMP (last menstrual period) 2015.8.29 PRL (prolactin) = 92.92 ng/ml 2015.10.22 Risperidone 2 mg/d+ Aripiprazole 10 mg/d X 21 days 2015.11.12 Risperidone 1 mg/d+ Aripiprazole 20 mg/d X 14 days 2015.11.26 Aripiprazole 20 mg/d (delete risperidone) 2015.12.16 PRL = 6.93 ng/nl 2016.2.4 PRL = 6.65 ng/nl	2016.8.7 LMP 2016.10.18 Zotepine 50 mg/d+ Aripiprazole 10 mg/d+ Lithium 600 mg/d 2016.10.19 PRL = 8.01 ng/ml 2016.10.26 Aripiprazole 20 mg/d+ Lithium 600 mg/d (delete zotepine) 2016.11.4 PRL = 5.42 ng/ml 2016.11.14 Norethisterone (5) 1#tid x 3 days (progestin challenge) 2016.11.15 Normal CEA/CA125; CEA (carcinoembryonic antigen); CA (carbohydrate antigen) r/o ovarian cancer
Result	2015.12.15 Menstruation resumed naturally without assistance from gynecological drugs, and body weight decreased by 3-4 kilograms	2016. 11.22 Menstruation resumed

In conclusion, when using antipsychotics among premenopausal women, we should consider the possibility of self-discontinuation of medications due to amenorrhea. Hence, after achieving rapid symptom alleviation using non-aripiprazole antipsychotics, the patient should be switched to aripiprazole, which prevents amenorrhea and may also achieve weight loss. Further clinical studies are needed to explore possible solutions to amenorrhea induced by antipsychotics. Figure 1 summarizes the clinical algorithm used when patients are suspected of antipsychotic-induced amenorrhea[7].

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