Letter to the Editor
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Amenorrhea as a Side Effect of Low Dose Aripiprazole: An Adolescent Case

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TO THE EDITOR

Guler *et al.*[1] have recently reported an interesting case of amenorrhea in the setting of an adolescent girl with major depressive disorder (MDD) being treated with fluoxetine (FLUX) 40 mg and aripiprazole (ARIP) 5 mg/day. Few points are noteworthy mentioning here.

Although a modicum of evidence-base might support combination-initiation therapy in MDD, polypharmacy from the outset with an add-on AAP cannot be justified on clinical grounds especially in absence of psychosis or suicidality as the case portrays. Injudicious use of AAPs is currently rampant and sorely off-label driven. This practice is perilous and use is fraught with drastic cardio-metabolic and neuro-hormonal syndromes with child and adolescent psychiatric (CAP) population being at heightened risk by virtue of age.[2]

ARIP is lauded for a metabolic-friendly profile, but this is not typically the case in CAP population.

True and rightful that ARIP at low dose has been deployed in clinical practice to treat risperidone-induced hyperprolactinemia (hPRL) through partial D2/D3 agonism and 5-HT2A antagonism releasing dopamine in the tubero-infundibular pathway. Whilst rare, yet reports of paradoxically ARIP-induced hPRL abound in literature.[3]

Onset of hPRL can take place theoretically in 24 hours following a single dose of ARIP. Mechanistically, what is needed is to occupy 72% of D2 receptors in the tubero-infundibular pathway (anatomically projecting from arcuate nucleus to median eminence). ARIP is notorious to have D2 *tenacity*. This pharmacodynamics property can give rise to extrapyramidal syndromes and hPRL at these relatively small doses.

Selective serotonin reuptake inhibitors (SSRIs), by virtue of 5HT2 agonism can cause akathisia and hPRL on its own merits.[4] So, FLUX at 40 mg/day in this case might have contributed to this side effect.

As indicated by authors, FLUX is a potent CYP 2D6 inhibitor and since ARIP is partly a substrate of 2D6 (and also 3A4). This 'combo' can push up ARIP levels causing higher blockade and accordingly likelihood of hPRL.

As there was no genotyping for the case, a remote possibility of 2D6 slow metabolizer (5-10% of Caucasians) cannot be confidently ruled out/in and might contribute to the incident reported here.

Last but not least, high levels of anxiety as reflected in this case have been classically cited as a cause of hPRL in unmedicated subjects.[5]

It behooves clinicians then to be more vigilant and cognizant of ARIP+SSRI combination in clinical practice. This 'combo' can be associated with higher D2 blockade and potential side effects.

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