

## A Comment on “Add-on Aripiprazole for Atypical Antipsychotic-induced, Clinically Significant Hyperprolactinemia”

Sir,

Use of add-on aripiprazole (ARIP) for antipsychotic-induced hyperprolactinemia (hPRL) is currently an increasingly deployed strategy on clinical grounds. Sound evidence base supports this approach, and this is replicated in the current study.<sup>[1]</sup> Having said so, a few comments are worthy of mention.

1. Although it sounds rational, this is an exemplar of antipsychotic polypharmacy,<sup>[2]</sup> and cost-effectiveness should be factored in
2. This strategy might be superior to swapping to PRL-sparing antipsychotic only when the patient is symptomatic, and there seems a risk to compromise the therapeutic response
3. This strategy has been proven to be efficacious with risperidone-induced hPRL more than amisulpride-induced hPRL<sup>[3]</sup>
4. Use of long-acting injectable forms has been noted to be associated with lower levels of hPRL than oral forms.<sup>[4]</sup> This might be a reasonable option, especially when compliance is questionable
5. Although not that much, tolerance to antipsychotic-induced hPRL has been demonstrated. The plateau occurs commonly in the 4<sup>th</sup> month, with a decline of levels thereafter.<sup>[5]</sup> Hence, if the patient is asymptomatic, monitoring serum prolactin and “wait-and-see” strategy might make better sense
6. Doses of ARIP in this study,  $13.8 \pm 7.4$  mg/day, are a sort of higher than usually used. Doses above 6 mg/d were not found to be any better<sup>[6]</sup>
7. Mechanistically, D2/D3 partial agonism by ARIP can explain this indication. However, 5-HT<sub>2A</sub> antagonism is also contributory, boosting DA tone in the tuberoinfundibular pathway<sup>[7]</sup>
8. Use of dopaminomimetic agents instead, albeit in theory might be psychotomimetic, has been demonstrated to be an effective without psychotic decompensation.<sup>[8]</sup> Use of bromocriptine, in particular, is advantageous, by virtue of antidiabetic actions, to mitigate other metabolic parameters induced by atypical antipsychotics, to alleviate extrapyramidal side effects, and to help with negative domain schizophrenia<sup>[9]</sup>
9. Most importantly, especially when ARIP is used at high-dose ranges, this regimen might result in “pharmacodynamic failure” and “pharmacologic relapse.”<sup>[10]</sup> ARIP is notorious for D2 tenacity. It would compete and eventually displace risperidone, and it would be more of D2 partial agonist (30% of DA agonism) “stabilizing DA” at receptor landscape counterbalancing DA blockade by risperidone in the first place and as such compromising previous therapeutic response. It then behooves clinicians to be mindful of these “combs” that might be unwittingly contribute to treatment failure (or pseudoresistance)
10. While rare, reports of paradoxically ARIP-induced hPRL abound in literature.<sup>[11]</sup>

Moreover, hPRL was reported in prodroma phase and untreated schizophrenics.<sup>[12]</sup>

The bottom-line is that aripiprazole is neither ambrosia nor panacea!

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### Conflicts of interest

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