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COMMENTARY

Response to *"Clomipramine in Combination with Fluvoxamine: A Potent Medication Combination for Severe or Refractory Pediatric OCD"*

Ryan Fung BSP, ACPR[1]; Dean Elbe PharmD, BCPP[2]; S. Evelyn Stewart MD, FRCPC[3]

We appreciate the concerns brought forward in the commentary "Clomipramine in Combination with Fluvoxamine: a Potent Medication Combination for Severe or Refractory Pediatric OCD" (Hardy & Walkup, 2021). We wish to reiterate that, due to the complexities in managing severe or refractory pediatric obsessive-compulsive disorder (OCD), further study is warranted to determine the best approach to pharmacotherapy, and, particularly, combination pharmacotherapy.

Our paper reported on safe use of fluvoxamine (FLV) and clomipramine (CMI) combination in a series of individuals with pediatric OCD (Fung, Elbe, & Stewart, 2021). In addition, we proposed a novel, efficient and safe approach to initiating combination therapy in pediatric OCD. Combined use of FLV-CMI that begins with FLV then adds CMI enables a lower final dosage of CMI and less exposure to desmethylclomipramine (DCMI) related adverse effects, in addition to providing a time efficient approach. Our proposed strategy for implementing and optimizing combination pharmacotherapy follows the current, evidence-based guidelines and standards of care for treating severe pediatric OCD that begins with two selective serotonin reuptake inhibitors (SSRIs) monotherapy trials (Fineberg et al., 2020; Geller, March, & AACAP Committee on Quality Issues, 2012). It is guided by the extant body of evidence denoting SSRI efficacy and safety in adult and pediatric OCD, but also incorporates a balanced approach that acknowledges greater response rates but poorer tolerability of CMI versus SSRIs (Fung, Elbe & Stewart, 2021). As noted in step 4 of our algorithm, serum CMI and DCMI concentration analysis and ECGs are to be performed routinely with dosage adjustment, and implicit to this statement is that CMI and/or fluvoxamine FLV dosages will be adjusted to maintain safety and efficacy parameters.

Hardy and Walkup describe alternative approaches to initiating combination FLV-CMI pharmacotherapy:

1a) ***The commentary authors Hardy and Walkup recommend for patients with previously failed SSRI trials or severe symptoms to "subsequently start with CMI" then add FLV. This would be in line with current monotherapy guidelines for refractory OCD***. We respectfully argue that, in light of our findings, this approach could be further optimized and made more efficient by subsequently adding CMI to FLV.

[1]Clinical Pharmacist, Saskatchewan Health Authority, Saskatoon, Saskatchewan (formerly, Pharmacy Resident, Department of Pharmacy, Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia)
[2]Clinical Pharmacy Specialist, Department of Pharmacy, Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia; Child and Adolescent Mental Health Programs, BC Children's Hospital, Vancouver, British Columbia; Department of Psychiatry, University of British Columbia, Vancouver, British Columbia
[3]Director, Provincial OCD Program, BC Children's Hospital; Research Director, Child, Youth and Reproductive Mental Health Programs, BC Children's Hospital; Professor of Psychiatry, Faculty of Medicine, University of British Columbia.

Given inter-patient variability (as demonstrated in Figure 1 of our paper) and the potential for saturable CMI pharmacokinetics, risks of unintentionally exceeding safe levels of CMI are higher when adding FLV to therapeutic levels of CMI than vice-versa (i.e. adding CMI to therapeutic levels of FLV). This order (CMI and then FLV) could also lead to DCMI concentrations that greatly exceed CMI concentrations, potentially resulting in toxicity, and, as such, may be a more poorly tolerated approach.

1b) ***For patients with severe OCD symptoms and no previous medication trials, Hardy and Walkup suggest starting with CMI then adding FLV. They suggest using an ultra-low dose of FLV (between 2.5-10 mg/day)***. This approach deviates completely from current treatment guidelines (Geller et al., 2012), given the added risk of CMI as an initial medication trial versus an SSRI. Additionally, in Canada, fluvoxamine is only available in 50 mg and 100 mg tablets, so the suggestion to use an "ultra-low dose" adds an extra barrier to the provision of care (e.g., the patient would require a compounded product, which may not be accessible locally and would increase drug costs).

2) ***In the second alternative, Hardy and Walkup suggest starting with FLV as the first SSRI then subsequently adding CMI.*** While not unreasonable, this approach may lead to unnecessary use of a medication with greater potential toxicity and impose an unnecessary burden on the child and family (due to the requirement for laboratory monitoring in clomipramine and not SSRIs), given evidence exists to show a 40% response rate to a second SSRI trial in OCD (Szegedi, Wetzel, Leal, Härrter, & Hiemke, 1996).

3) ***In the third alternative, Hardy and Walkup suggest that a "less ideal" option would be initiating combination FLV-CMI therapy as the first pharmacotherapy trial.*** There is currently no evidence to support this approach. It assumes that monotherapy is ineffective, and it ignores current evidence-based guidelines (Geller et al., 2012). The commentary authors themselves state that this would lead to uncertainty in adjusting the medications. Furthermore, the use of two medications where one could suffice predisposes patients to an increased risk of side effects and increased drug costs (i.e., it presents very real barriers to treatment). If the patient did not tolerate one of the medications, it would be difficult to determine the offending agent and the patient may then refuse both medications, even if one may have provided benefit while the other was intolerable. Consequently, a step-wise approach is much more likely to be successful.

We would like to thank the commentary authors for expressing their concerns and allowing us the opportunity to demonstrate how our proposed algorithm for pediatric OCD strikes a safe, practical, and balanced approach between evidence-based medicine and patient-centred care for this challenging patient population.

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