JOURNAL
OF THE CANADIAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY / DE L'ACADÉMIE CANADIENNE DE PSYCHIATRIE DE L'ENFANT ET DE L'ADOLESCENT

COMMENTARY

Clomipramine in Combination with Fluvoxamine: A Potent Medication Combination for Severe or Refractory Pediatric OCD

Nathan E. Hardy MD[1]; John T. Walkup MD[1]

Abstract

Clomipramine (CMI) and fluvoxamine (FLV) combination therapy has been shown in adults to be a potent medication strategy for obsessive compulsive disorder (OCD). Fung et al. (2021) is the first to show similar benefit in pediatric OCD. The addition of FLV to CMI inhibits the metabolism of clomipramine to desmethylclomipramine (DCMI) and enhances the serotonergic potency of CMI by shifting the routine ratio of CMI<DCMI to CMI>DCMI via inhibition of the CYP450 system. The approach to CMI+FLV combination therapy outlined by Fung et al. requires close monitoring. This commentary reviews the benefits and challenges of the approach of Fung et al. (2021) and provides other strategies to take advantage of this combination. Clinicians may consider starting with CMI and adding FLV for patients with refractory OCD to offer a faster pathway to potentially more effective treatment. If a clinician prefers starting with SSRI monotherapy, choosing FLV initially allows for a simpler transition to CMI+FLV in the event that SSRI monotherapy fails.

Key Words: *obsessive compulsive disorder, clomipramine, fluvoxamine, psychopharmacology*

Résumé

La thérapie de combinaison de la clomipramine (CMI) et de la fluvoxamine (FLV) s'est révélée chez les adultes une stratégie médicamenteuse puissante pour le trouble obsessionnel-compulsif (TOC). Fung et coll. est le premier à montrer un bénéfice semblable dans le TOC pédiatrique. L'ajout de FLV à la CMI inhibe le métabolisme de la clomipramine pour la desméthylclomipramine (DCMI) et augmente la puissance sérotoninergique de la CMI en changeant le rapport régulier de CMI<DCMI pour CMI>>DCMI au moyen de l'inhibition du système CYP450. L'approche de la thérapie de combinaison CMI+FLV présentée par Fung et coll. nécessite une surveillance étroite. Le présent commentaire révise les avantages et les difficultés de l'approche de Fung et coll. et offre d'autres stratégies pour profiter de cette combinaison. Les cliniciens peuvent songer à commencer avec la CMI puis à ajouter la FLV pour les patients souffrant d'un TOC réfractaire afin de leur offrir une trajectoire plus rapide vers un traitement possiblement plus efficace. Si un clinicien préfère commencer par une monothérapie d'ISRS, choisir la FLV au départ permet une transition plus simple à CMI+FLV au cas où la monothérapie d'ISRS ne fonctionne pas.

Mots clés: *trouble obsessionnel compulsif, clomipramine, fluvoxamine, psychopharmacologie*

[1]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA

Corresponding E-Mail: JWalkup@luriechildrens.org

Submitted: January 7, 2021; Accepted: July 12, 2021

Introduction

Managing pediatric obsessive-compulsive disorder (OCD) can be challenging, as an inadequate response to first-line treatments is common. Although cognitive behavioral therapy (CBT) is considered the first-line treatment for OCD, medication may be necessary when CBT is unavailable or when OCD symptoms are so severe that a patient is unable to fully engage in CBT. In pediatric OCD treatment guidelines, selective serotonin reuptake inhibitors (SSRI), including fluvoxamine (FLV), sertraline, and fluoxetine, are considered first line due to demonstrated safety and efficacy (Geller & March, 2012). While the serotonin reuptake inhibitor (SRI) clomipramine (CMI) is often thought to be more effective than the SSRIs, it is considered second-line given its less favorable side effect profile and the need for close monitoring (Geller et al., 2003; Geller & March, 2012; Watson & Rees, 2008).

One general concern with SRI or SSRI monotherapy for OCD is inadequate response in short term studies. The SRIs are clearly more effective than placebo, but they often leave patients with clinically meaningful OCD symptoms even after 12-13 weeks of treatment. With extended treatment, patients can continue to improve out to 20 weeks but may remain symptomatic (Cook et al., 2004). What then is the management approach to refractory, partially responsive, or severe pediatric OCD? While switching SRIs is a commonly recommended next step, expert guidelines also suggest the potential value of adding a second medication (March et al., 1997).

In the last issue of the *Journal of Canadian Child and Adolescent Psychiatry*, Fung et al. reported on one pharmacologic approach to severe pediatric OCD using the combination of clomipramine and fluvoxamine (Fung et al., 2021). The approach was first described in a case series of adults with OCD (Szegedi et al. 1996) and takes advantage of a CYP450 drug interaction to improve the serotonergic impact of clomipramine. Fung et al. provide an excellent review of clomipramine and fluvoxamine metabolism and share their clinical experience using these medications in combination. In this commentary, we provide a brief review of clomipramine and fluvoxamine metabolism, a commentary on Fung et al.'s approach to implementing CMI+FLV combination therapy, and a discussion on several alternative strategies for implementing combination CMI+ FLV pharmacotherapy for treatment refractory OCD.

Clomipramine Pharmacokinetics

Clomipramine, a tricyclic antidepressant, was the first medication approved by the Food and Drug Administration (FDA) for OCD; it was also approved by Health Canada for OCD treatment for children age ten and older. The benefits of clomipramine in treating OCD are thought to be due to clomipramine's potent serotonergic activity, and meta-analyses suggest clomipramine may be superior to SSRIs in the treatment of OCD (Geller et al., 2003; Watson & Rees, 2008).

Clomipramine undergoes extensive first-pass metabolism in the liver to desmethylclomipramine (DCMI) by CYP1A2, CYP2C19, and CYP3A4. The CMI molecule is a potent serotonin reuptake inhibitor, but DCMI has minimal serotonergic activity and potent noradrenergic activity. DCMI is ultimately metabolized by CYP2D6. At steady state the ratio of CMI to DCMI is roughly 1:2-3 because CMI has a half-life of 12-36 hours and DCMI has a half-life of approximately 72 hours. Thus, after oral administration, much of the therapeutic effect of CMI's serotonergic activity is lost and replaced by the noradrenergic activity of DCMI. One novel approach to maximize the serotonergic activity of CMI is to administer clomipramine intravenously, avoiding first-pass metabolism and maximizing the serotonergic activity of CMI at the level of the brain (Koran et al., 1997). The approach by Fung et al. seeks to mimic the effects of intravenous administration of CMI by oral administration of the CMI+FLV combination.

Psychiatrists should be aware that CYP450 activity is strongly influenced by genetic variation and this could account for differences in clomipramine dosage requirements and adverse effects across patients.

Fluvoxamine and its impact on Clomipramine Metabolism

Fluvoxamine is an FDA approved SSRI for the treatment of OCD in children and adults and it is also approved by Health Canada for OCD treatment for people age 18 and older. Fluvoxamine (FLV) inhibits CYP1A2, CYP2C19, and CYP3A4 – the very isoenzymes involved in the metabolism of CMI to DCMI. The coadministration of CMI and FLV results in the inhibition of CMI to DCMI metabolism and shifts the ratio of CMI < DCMI to CMI > DCMI.

Importantly, other SSRIs do not share this unique interaction. Many prescribers view SSRIs as interchangeable; however, caution should be taken when prescribing clomipramine with SSRIs other than fluvoxamine, particularly

those that significantly inhibit CYP2D6 (e.g. fluoxetine and paroxetine). Because DCMI is metabolized by CYP2D6, CMI in combination with fluoxetine or other 2D6 inhibitors leads to increased serum concentration of DCMI, an even greater DCMI >> CMI ratio, and increased risk for undesirable adrenergic effects.

Interestingly, patients who have CYP2D6 hypometabolism because of genetic variation may be at increased risk of build-up of DCMI, which could be managed by CMI+FLV combination therapy. Finally, while FLV is a potent inhibitor of CYP1A2, CYP2C19, and CYP3A4, it is also a weak 2D6 inhibitor. Thus, the combination of CMI+FLV improves the ratio of CMI>DCMI, but also increases overall blood level of CMI+DCMI.

Fung et al.'s Strategy for Combining Fluvoxamine and Clomipramine

Fung et al. describe an approach to FLV+CMI combination therapy that begins with a trial of a non-FLV SSRI. If the first SSRI is not effective, they then recommend an adequate trial of FLV. If FLV is ineffective, they next recommend slowly adding CMI until the CMI:DCMI ratio is >3 and still within the therapeutic range of CMI + DCMI ≤ 450 ng/mL. In their case series, this resulted in a mean end point doses of FLV 112.5 mg/day and CMI 87.5 mg/day. They also provide important guidance on monitoring blood pressure, heart rate, EKGs, and medication levels.

Fung et al. provide one strategy for combining CMI and FLV, and we would like to highlight potential challenges within the steps of their approach.

1. Their first step requires a full trial with a non-FLV SSRI, which is standard care for pediatric OCD. The challenge is that this initial step alone may require several months to reach maximum dosage and maximum benefit before results can be fully evaluated. Children and adolescents can sometimes tolerate upwards of fluoxetine 40-60 mg/day or sertraline 100-200 mg/day, and as mentioned above it is common for symptoms to be reduced over the first 12-13 weeks but for patients to remain substantially symptomatic until 16-20 weeks of SSRI monotherapy (March et al. 1997). It is critical that this first step be implemented effectively with adequate dose and adequate duration of treatment before changing medication. If OCD symptoms are severe or the patient has previously failed SSRI trials, the clinician may want to initiate an arguably more efficacious treatment.
2. If the non-FLV SSRI is deemed to be ineffective, Fung et al. recommend a switch from the initial SSRI (presumably at maximum tolerated dose) to FLV. This transition can be managed by discontinuing the first SSRI, letting it clear and then starting the second SSRI. This approach has the potential for some loss of OCD symptom control after tapering the first SSRI and while waiting for the second SSRI to become effective. To avoid this, clinicians can choose to cross taper the two SSRIs. Cross tapering may still result in a loss of existing OCD control if the first SSRI is discontinued too quickly. Cross tapering also requires careful monitoring for both benefits and side effects. During a cross taper, there are two SSRIs interacting, and interestingly, one treatment strategy for refractory or partially responsive OCD is to purposely use two SSRIs (March et al. 1997). The clinician needs to remain alert during a cross taper as the patient may experience some increased benefit when on both SSRIs. If that were to occur the clinician may actually choose to not complete the cross taper to maintain the benefit of the interacting SSRIs. That said, using two SSRIs also increases the need for monitoring for serotonin side effects. In short, tapering or cross tapering are complex strategies, particularly for children and adolescents. While commonly implemented in clinical practice, strategies that avoid the need for cross tapering might be useful.
3. The third step, when FLV monotherapy is deemed ineffective or only partially effective, is the addition of clomipramine. It is presumed that the dose of FLV was maximized before considering adding CMI but given average end point doses of FLV 112.5 mg/day reported by Fung et al. it is unclear if FLV ever reached maximum tolerated dose given the clinical maximum dose of fluvoxamine is 200mg. It is also unclear if FLV was reduced as CMI was added and increased.

Other Strategies for Combining Clomipramine and Fluvoxamine

Below, we review three other approaches to arrive at CMI and FLV combination therapy for when the patient has treatment-refractory illness. As stated above, CBT is first line for OCD and should be available for those with severe and refractory illness at a level that addresses the patient's needs and capacities. That said, when CBT has been maximized and symptoms remain due to lack of insight, gross impairment, or inability to participate in exposure therapy, the pharmacologic strategy listed here may be helpful for patients who have failed other pharmacologic strategies as well as CBT.

The three strategies differ from current guidelines of starting pharmacotherapy with a non-FLV SSRI and would be best implemented by expert clinicians in a higher level of care, such as an intensive outpatient program or inpatient unit. Different augmentation strategies should be pursued given the right circumstance, such as the use of SSRI augmentation with an antipsychotic for those with obsessive-compulsive behavior and a comorbid tic disorder (McDougle et al., 1994).

For each of these alternatives, a full medical work-up and the capacity to monitor vital signs, EKGs, blood levels, adherence and outcomes is required. It is worth reiterating that combining CMI and a non-FLV SSRI with CYP2D6 inhibition is not recommended, as this would lead to a build-up of DCMI and increased risk of adrenergic side effects or events in addition to being counterproductive to increasing the serotonergic impact of CMI. It is important to remind clinicians that clomipramine can have impact on cardiac function. Careful monitoring is required and it may be inadvisable or contraindicated to use CMI in those patients with cardiac conduction abnormalities, hypertension, or tachycardia, and in patients with history of seizure. Additional care should be taken if the patient is already on medications that alter CYP450 metabolism.

A. For cases where OCD symptoms are severe or where the patient has had unsuccessful trials of SSRI in the past, consider starting clomipramine from the beginning of treatment. The logic of starting CMI first is to offer the patient the most efficient approach to arguably the most potent pharmacologic strategy for severe OCD. If symptoms are still present at the maximum tolerated CMI dose after an adequate length of time to see benefit, low dose FLV can be added to improve CMI potency and side effect profile. Starting with CMI would involve performing a baseline medical work up, then initiating CMI and adjusting to maximum tolerated dose of up to 3mg/kg, 200 mg/daily, or to maximum blood level. At clomipramine's maximum tolerated dose or blood level, another EKG should be performed, and fluvoxamine could then be started at an ultralow dose (between 2.5-10mg) to shift the CMI:DCMI ratio from CMI<DMCI to CMI>DCMI while keeping the combined concentration less than 450 ng/mL. At each FLV dose change, follow-up blood levels and EKG should be obtained, and adequate time should be taken to monitor for clinical benefit. A potential drawback of starting with CMI is the risk for CMI<<DCMI side effects early in treatment before FLV is added to modulate the CMI>>DCMI ratio.

B If the clinician prefers SSRI monotherapy as a first step, consider starting fluvoxamine at the beginning of treatment, rather than waiting for a failed trial of another SSRI. Patients may be more inclined to start with SSRI rather than CMI, but if symptoms are still severe after an adequate trial of FLV, clomipramine could be added at low dose (typically between 6.25-25mg/daily) after the necessary medical evaluation. This method would result in a therapeutic dose of FLV and CMI>DCMI ratio, but a subtherapeutic total concentration of CMI+DCMI. However, even if the CMI+DCMI concentration is low, such serotonergic augmentation of an SSRI may have synergistic effects (March et al. 1997) similar to the hypothesized mechanism of lithium augmentation of antidepressants in refractory depression (Barowsky et al., 2006). If the patient's symptoms do not go into remission on FLV and low-dose clomipramine, the clinician may make further adjustments and transition to high dose CMI and low dose FLV to mimic the strategy described in Section A above. A drawback to this strategy is the work required to transition two medications while monitoring closely for benefits, side effects, blood levels, and EKG changes.

C. For completeness, a third option, which is less ideal, is to start clomipramine and fluvoxamine together at the beginning of treatment after a baseline medical evaluation and EKG. This would allow for CMI>DMI at the beginning of treatment. However, this approach creates

uncertainty in when and how to adjust the combination. Without establishing a patient response to one medicine, a clinician may not confidently know which medication to adjust. If this third method is chosen and both medicines are started at low dose, it would be most logical to increase clomipramine first to the maximum tolerated dose with an adequate trial, then increase fluvoxamine for the reasons described in Section A. Again, between dose changes, the clinician must check blood levels and an EKG, and evaluate clinical benefit over an adequate length of time before adjusting dose again.

Summary

While clomipramine and fluvoxamine combination therapy has been known for decades, Fung et al. is the first to show that the CMI:DCMI ratio can be modulated by fluvoxamine to optimize CMI levels in the treatment of pediatric OCD. The approach to combination therapy outlined by Fung et al. requires close monitoring, but it is most accessible to the clinician who is most familiar with starting a non-FLV SSRI as a first medication for OCD. For patients with severe OCD, clinicians could plan to utilize combination therapy from the beginning of treatment. Starting with clomipramine and then introducing fluvoxamine if clomipramine is ineffective may be the most practical way to implement this potent serotonergic combination. If a clinician prefers starting with SSRI monotherapy, choosing FLV allows for a simple transition to combination therapy in the event that SSRI monotherapy fails.

Conflicts of Interest

The authors have no financial relationships to disclose.

References

Barowsky, J., & Schwartz, T.L. (2006). An Evidence-Based Approach to Augmentation and Combination Strategies for: Treatment-Resistant Depression. *Psychiatry (Edgemont (Pa.: Township))*, *3*(7), 42-61.

Cook, E.H., Wagner, K.D., March, J.S., Biederman, J., Landau, P., Wolkow, R., & Messig, M. (2001). Long-term sertraline treatment of children and adolescents with obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*(10), 1175-1181. https://doi.org/10.1097/00004583-200110000-00011

Fung, R., Elbe, D., & Stewart, S.E. (2021) Retrospective Review of Fluvoxamine-Clomipramine Combination Therapy in Obsessive-Compulsive Disorder in Children and Adolescents. *Journal of Canadian Child and Adolescent Psychiatry*, To Be Published.

Geller, D.A., Biederman, J., Stewart, S.E., Mullin, B., Martin, A., Spencer, T., & Faraone, S.V. (2003). Which SSRI? A meta-analysis of pharmacotherapy trials in pediatric obsessive-compulsive disorder. *The American Journal of Psychiatry*, *160*(11), 1919-1928. https://doi.org/10.1176/appi.ajp.160.11.1919

Geller, D.A., & March, J. (2012). Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(1), 98-113. https://doi.org/10.1016/j.jaac.2011.09.019

Koran, L.M., Sallee, F.R., & Pallanti, S. (1997). Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. *The American Journal of Psychiatry*, *154*(3), 396-401. https://doi.org/10.1176/ajp.154.3.396

March, J., Frances, A., Carpenter, D., & Kahn, D. (1997). Treatment of obsessive-compulsive disorder: The Expert Consensus Panel for obsessive-compulsive disorder. *The Journal of Clinical Psychiatry*, *58* Suppl 4, 2-72. PMID: 9183300.

McDougle, C.J., Goodman, W.K., & Price, L.H. (1994). Dopamine antagonists in tic-related and psychotic spectrum obsessive compulsive disorder. *The Journal of Clinical Psychiatry*, *55 Suppl*, 24-31.

Szegedi, A., Wetzel, H., Leal, M., Härtter, S., & Hiemke, C. (1996). Combination treatment with clomipramine and fluvoxamine: Drug monitoring, safety, and tolerability data. *The Journal of Clinical Psychiatry*, *57*(6), 257-264.

Watson, H.J., & Rees, C.S. (2008). Meta-analysis of randomized, controlled treatment trials for pediatric obsessive-compulsive disorder. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *49*(5), 489-498. https://doi.org/10.1111/j.1469-7610.2007.01875.x