

RESEARCH ARTICLE

Retrospective Review of Fluvoxamine-Clomipramine Combination Therapy in Obsessive-Compulsive Disorder in Children and Adolescents

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Abstract

Objectives: To inform dosing and describe the pharmacokinetic interaction, efficacy and safety of fluvoxamine-clomipramine combination therapy for treatment-resistant pediatric obsessive-compulsive disorder (OCD).

Methods: A retrospective chart review of OCD-affected patients at a tertiary care children's hospital between January 2010 and August 2017 was conducted. Those included were 18 years of age or younger at initiation of fluvoxamine-clomipramine combination therapy and had at least one set of serum concentration values capturing clomipramine and desmethylclomipramine levels. **Results:** Six adolescents met study inclusion criteria. Fluvoxamine adequately inhibited clomipramine metabolism to desmethylclomipramine in a dose-dependent manner. Fluvoxamine-clomipramine combination therapy was generally well tolerated with no serious or life-threatening adverse effects reported. **Conclusion:** Fluvoxamine-clomipramine combination therapy permits use of lower clomipramine doses than typically used as clomipramine monotherapy and appears to be a safe alternative for pediatric OCD patients failing sequential selective serotonin reuptake inhibitor monotherapy trials. Inter-patient variability and saturable kinetics support therapeutic drug monitoring of serum clomipramine and desmethylclomipramine concentrations to optimize therapy. A proposed algorithm that aligns with current OCD treatment guidelines is described. Further study is needed to evaluate efficacy of this approach.

Key Words: *obsessive-compulsive disorder, pediatric, adolescent, fluvoxamine, clomipramine*

Résumé

Objectifs: Préciser la posologie et décrire l'interaction pharmacocinétique, l'efficacité et l'innocuité de la thérapie combinée fluvoxamine-clomipramine pour le trouble obsessionnel-compulsif (TOC) pédiatrique réfractaire au traitement. **Méthodes:** Une revue de dossiers rétrospective de patients souffrant du TOC à un hôpital pour enfants de soins tertiaires entre janvier 2010 et août 2017 a été menée. Les patients inclus avaient 18 ans ou moins lors de l'initiation de la thérapie

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combinée fluvoxamine-clomipramine et avaient au moins une série de valeurs de concentration sérique pour le captage des taux de clomipramine et de desméthylclomipramine. **Résultats:** Six adolescents satisfaisaient aux critères d'inclusion de l'étude. La fluvoxamine inhibait adéquatement le métabolisme de la clomipramine pour la desméthylclomipramine de manière dose-dépendante. La thérapie combinée fluvoxamine-clomipramine était généralement bien tolérée sans effets indésirables sérieux ou dangereux déclarés. **Conclusion:** La thérapie combinée fluvoxamine-clomipramine permet d'utiliser des doses plus faibles de clomipramine que celles habituellement utilisées en monothérapie de clomipramine et semble être une solution de rechange sûre pour les patients du TOC pédiatrique qui ne répondent pas aux essais de monothérapie d'inhibiteurs sélectifs séquentiels de recaptage de la sérotonine. La variabilité inter-patients et la cinétique saturable soutiennent le contrôle des médicaments thérapeutiques et des concentrations sériques de clomipramine et de desméthylclomipramine afin d'optimiser la thérapie. Un algorithme proposé qui correspond aux lignes directrices du traitement du TOC est décrit. Il faut d'autres études pour évaluer l'efficacité de cette approche.

Mots clés: *trouble obsessionnel-compulsif, pédiatrique, adolescent, fluvoxamine, clomipramine*

Introduction

Obsessive-compulsive disorder (OCD) in children and adolescents affects approximately 2% of the population, is often undiagnosed, and can lead to significant disability, including impaired performance in school, family, and social domains (Geller, March, & AACAP Committee on Quality Issues, 2012). OCD presents with obsessions (distressing, repetitive thoughts, images or impulses), compulsions (repetitive behaviours or mental acts) or a combination of both (Geller et al., 2012). Severity of OCD can be rated on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), a validated clinician-rated questionnaire and the standard assessment tool in pediatric OCD (Geller et al., 2012; Scahill et al., 1997; Storch, Lewin, De Nadai, & Murphy, 2010). Scores range from 0 to 40 (extreme), based on responses to five questions each about obsessions and compulsions (Storch et al., 2010). Repeat administration of the CY-BOCS provides an objective index for monitoring patient progress and response to treatment (Scahill et al., 1997; Storch et al., 2010).

Exposure and response prevention therapy is the key component of cognitive behavioural therapy recommended as first-line treatment for mild to moderate OCD, while the addition of pharmacotherapy is indicated in more severe OCD (Geller et al., 2012).

As per international OCD guidelines, selective serotonin reuptake inhibitors (SSRIs) including fluvoxamine ([FLV]) are recommended first-line pharmacotherapy agents in moderate to severe illness (Geller et al., 2012, Fineberg et al., 2020). While generally less well tolerated than SSRIs, the tricyclic antidepressant clomipramine [CMI], a non-selective serotonin reuptake inhibitor is also identified as an evidence-based treatment (Geller et al., 2012, Fineberg et al., 2020). The adverse effect profile of CMI includes anticholinergic, histaminergic, adrenergic, and arrhythmogenic

effects, and typically preclude its use as initial therapy due to required electrocardiogram (ECG) and therapeutic drug monitoring (Geller et al., 2003; Geller et al., 2012). Consequently, CMI is generally reserved for patients failing monotherapy with one or more SSRIs (Geller et al., 2003; Geller et al., 2012). European guidelines similarly propose an SSRI trial prior to use of CMI (Fineberg et al., 2020). Although methodological differences exist in previous studies, an effect size of 0.85 was noted for CMI, which is larger than that of SSRIs in the treatment of pediatric OCD (Geller et al., 2003; Geller et al., 2012). As such, approaches that enable improved tolerability of CMI are worth consideration.

Clomipramine undergoes hepatic metabolism via cytochrome P450 (CYP) enzymes to desmethylclomipramine (DCMI), 8-hydroxy-CMI, and 8-hydroxy-DCMI. CYP1A2, CYP2C19, and CYP3A4 produce DCMI, a major and pharmacologically active metabolite with increased adrenergic and cardiotoxic potential (Balant-Gorgia, Gex-Fabry, & Balant, 1991; Conus, Bondolfi, Eap, Macciardi, & Baumann, 1996; Szegedi, Wetzel, Leal, Härter, & Hiemke, 1996). Mean half-lives of CMI and DCMI are approximately one day and three days, respectively (Balant-Gorgia et al., 1991). CYP2D6 produces inactive hydroxylated metabolites, which are conjugated and renally excreted (Balant-Gorgia et al., 1991; Conus et al., 1996; Szegedi et al., 1996). It has been suggested that CMI and DCMI metabolism may be saturable processes leading to nonlinear kinetics, particularly at the high end of the CMI dosing range in CYP2D6 poor metabolizers (Balant-Gorgia, Balant, & Zysset, 1987; Kuss & Jungkunz, 1986).

Fluvoxamine is a SSRI metabolized by CYP1A2 and CYP2D6 to inactive metabolites. It is also a potent inhibitor of CYP1A2 and CYP2C19, a moderate inhibitor of CYP2C9 and CYP3A4, and a weak inhibitor of CYP2D6 (Muscattello, Spina, Bandelow, & Baldwin 2012; Van Harten,

1995). Specifically, FLV-mediated inhibition of CYPs 1A2, 2C19, and 3A4 prevent formation of DCMI and lead to higher serum concentrations of CMI and its serotonergic properties. In contrast, inhibitors of CYP2D6, such as the commonly used SSRIs fluoxetine and sertraline, prevent the metabolism of DCMI, potentially leading to increased DCMI serum concentrations and increased side effects. The pharmacokinetic CYP interactions and cumulative effects on serotonin suggest the rational use of fluvoxamine-clomipramine combined therapy (FLV+CMI) in patients with OCD, while monitoring for serotonin syndrome. Serotonin syndrome results from excess serotonergic activity and presentations range from benign to fatal (Sun-Edelstein, Tepper, & Shapiro, 2008). Symptoms are temporally related to the addition or change in dose of serotonergic agents and include neuromuscular involvement, autonomic hyperactivity, and changes in mental status (Sun-Edelstein et al., 2008).

In a case series of 22 adults with OCD and depression, Szegedi et al. (1996) intentionally used FLV to inhibit the metabolic conversion of CMI to DCMI, presumably increasing the desired serotonergic effects and minimizing the treatment-limiting adrenergic side effects. Combination therapy was well tolerated in patients when the combined concentration of CMI and DCMI was less than 450 ng/mL and the ratio of DCMI:CMI concentrations was less than 0.3 (that is, when the serum concentration of CMI was 3.3 times greater than that of DCMI); no cases of serotonin syndrome were observed (Szegedi et al., 1996). Clinical efficacy was not evaluated, but this study suggested a safe and potential role for FLV+CMI (Szegedi et al., 1996).

There is currently no published literature pertaining to the use of FLV+CMI in children or adolescents with OCD.

Methods

Our exploratory research aimed to investigate the beneficial interaction and potential synergy of FLV+CMI to treat OCD in children and adolescents. We sought to describe the pharmacokinetics, dosing, efficacy, and safety of FLV+CMI, in order to inform a pharmacotherapeutic strategy for the management of treatment-resistant pediatric OCD. We performed a retrospective chart review of pediatric and adolescent patients with OCD at a tertiary children's hospital and its affiliated OCD outpatient program between January 2010 and August 2017. All patients 18 years of age or younger at initiation of FLV+CMI and who had at least one set of measurements of CMI and DCMI serum concentrations were included. Efficacy was defined as a 25% or greater decrease in CY-BOCS score, deemed a clinically significant response per the American Academy of Child

and Adolescent Psychiatry OCD Practice Parameter (Geller et al., 2012). Any documented adverse effect was included in the assessment of safety. Data were tabulated in Microsoft Excel and analysed with descriptive statistics of the aggregated data. Serum CMI and DCMI levels were analyzed via an in-house-developed assay set up and validated on Agilent 6470 liquid chromatography (LC)/mass spectrometry (MS)/MS triple quadrupole MS system using reagent kit "Tricyclic Antidepressants TCA 2 - LC-MS/MS" obtained from Chromsystems Instruments & Chemicals GmbH, Munich, Germany. Serum concentrations reported in nmol/L were converted to ng/mL in order to compare findings with those previously reported by Szegedi et al. (1996). The study protocol was approved by the hospital's research ethics board.

Results

Six adolescents met inclusion criteria (Table 1). A total of thirty-five sets of serum concentrations were included, with approximately 60% of the data being from two patients. The median peak daily doses of CMI and FLV were 87.5 mg and 112.5 mg, respectively (Table 2). Inhibition of DCMI formation appeared to be dependent on FLV dose, with FLV doses of at least 100 mg per day being required to attain the target DCMI:CMI ratio of 0.3 or less (Figure 1).

With the exception of a single asymptomatic excursion to a combined serum concentration (CMI+DCMI) of 505 ng/mL, patients were maintained below the safety threshold of 450 ng/mL as per Szegedi et al., 1996. Combination FLV+CMI was generally well tolerated in this cohort with no severe or life-threatening adverse effects and no adverse effect requiring dose reduction or cessation of therapy (Table 3). The prolonged QTc interval observed in a single patient was transient: in the minute prior and in subsequent ECG monitoring at the same doses, the QTc interval remained below 450 msec.

The ratios of the total combined serum concentration (CMI+DCMI) to CMI dose were analyzed with each measurement. One patient experienced a 1.8-fold increase in serum concentration-to-dose ratio over a 6-month period at the same doses of CMI and FLV, suggesting zero-order elimination of CMI in this patient.

CY-BOCS scores were reported for three patients. Two patients only had scores prior to FLV+CMI treatment. The remaining patient's score increased from 24 prior to FLV+CMI to 29 after 5 months of combination therapy, a 20% increase and still within the severe rating of the scale. The clinical significance of this change is unclear.

Discussion

For pediatric patients with treatment-resistant OCD, a trial of FLV+CMI combination therapy may be warranted. Present data suggest that FLV inhibits the metabolic conversion of CMI to DCMI in pediatric patients, theoretically maximizing the serotonergic effects of both medications while minimizing the treatment-limiting adrenergic adverse effects of DCMI. Although few patients achieved a DCMI:CMI serum concentration ratio of 0.3 or less, no significant adverse effects were described, which may suggest better tolerability in pediatric patients compared to adults. However, interpatient variability was observed, as demonstrated by the DCMI:CMI ratios of patients on CMI monotherapy (see Figure 1) and the patient demonstrating saturable kinetics. Consequently, therapeutic drug monitoring may have a role in assessing the extent of CYP inhibition and guiding therapeutic adjustments, and future studies to examine the impact of individual CYP genotypes may be warranted.

Dose-dependent sedation with FLV often requires twice daily administration, which may limit patient adherence to their medication regimen. FLV+CMI may allow for lower doses of both agents to be used, which could allow for once daily administration and increased adherence.

Based on these current findings, and in accordance with international guidelines proposing SSRI trials prior to CMI (Geller et al., 2012, Fineberg et al., 2020), our approach to the pharmacotherapeutic management of pediatric patients with moderate or severe OCD going forward will be as per Box 1.

The present study had many limitations. Firstly, this was a retrospective chart review with a small sample size. Data were not available for all patients at all points of therapy. Some of the data represented only the initiation of FLV+CMI, while other patients had data available up to 9 months of treatment. Additionally, three patients were 18 years of age at initiation and had few serum concentrations analyzed prior to graduating out of pediatric care and being lost to follow-up. Due to the retrospective nature of this study, online outpatient laboratory results were not available and may have contributed to the paucity of data for some patients. Medication administration record documentation of medication administration was assumed to be correct for inpatients, but adherence among outpatients could not be verified. Serum concentrations were ideally drawn 14 days after initiation or change in dose of either medication, in the morning, and 12 hours after the last dose was administered; however, the time of day at which samples were drawn was variable, particularly for outpatients.

Table 1. Patient characteristics

Patients (n)	6
Age, years, median (min-max)	15 (14-18)
Female, n (%)	3 (50)
Weight, kg, mean (SD)	52.5 (±10.6)
Number of prior SRI trials per patient, median (min-max)	2 (1-3)
Number of prior OCD augmentation trials per patient, median (min-max)	2 (0-3)
n number; OCD obsessive-compulsive disorder; SD standard deviation; SRI serotonin reuptake inhibitor	

Table 2. SRI dosing and serum concentrations

	n=6
Peak CMI dose, mg/day, median (min-max)	87.5 (50-150)
Peak FLV dose, mg/day, median (min-max)	112.5 (25-300)
Dose ratio, FLV:CMI, median (min-max)	1.2 (0.3-12)
Total serum CMI+DCMI, ng/mL, median (min-max)	223.7 (0-505.9)
Ratio of DCMI:CMI, median (min-max)	0.4 (0-3)
CMI clomipramine; DCMI desmethylclomipramine; FLV fluvoxamine; SRI serotonin reuptake inhibitor	

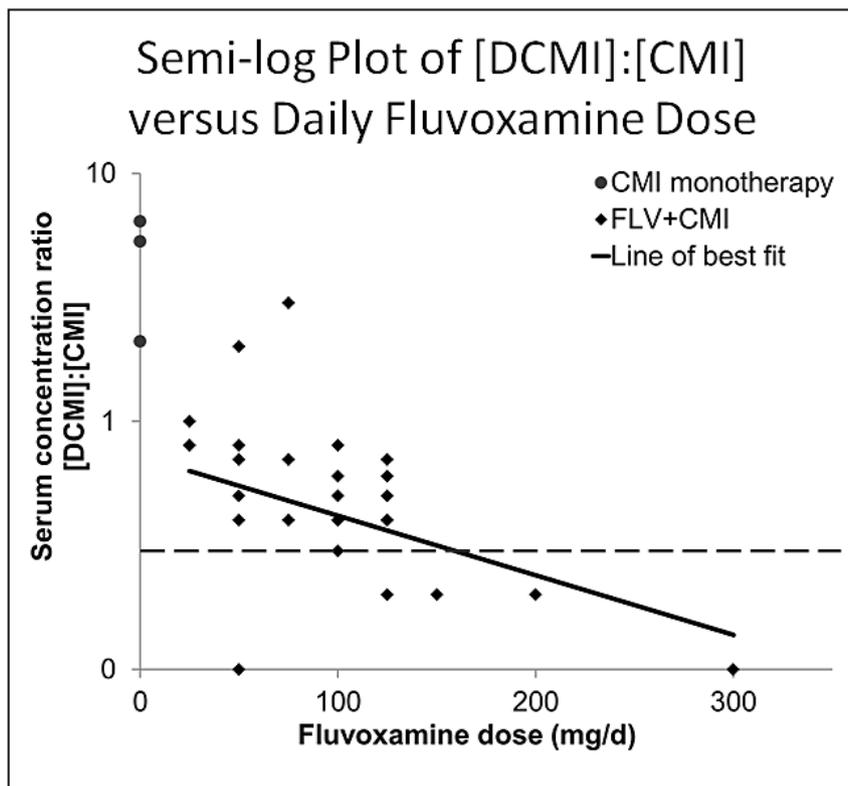
Table 3. Safety outcomes

	n=6
Patients experiencing ≥ 1 adverse effect, n (%)	3 (50)
Sedation, n (%)	1 (17)
Fatigue, n (%)	1 (17)
Dry mouth, n (%)	1 (17)
Constipation, n (%)	1 (17)
QTc > 450 msec, n (%)	1 (17)

As a retrospective chart review, this study was limited by what was documented. Efficacy could not be assessed due to poor reporting of CY-BOCS scores. Cigarette smoking, which can induce CYP1A2 enzymes and thus mitigate the effects of FLV, was poorly reported. It was unclear if the presence or improvement of adverse effects was regularly assessed.

Previously, there was no standard regimen for combining therapy with FLV and CMI, and patients in our study arrived at this combination via multiple pathways. Some patients had been transitioned from CMI monotherapy with the addition of FLV at low dose. Others had attained the maximum dose of FLV first and then were started on CMI. The remaining patients were transitioned from other SSRI monotherapy to low doses of both CMI and FLV.

Figure 1. Semi-log plot of [DCMI]:[CMI] versus daily fluvoxamine dose



Box 1. Proposed algorithm for the pharmacotherapeutic management of moderate to severe OCD in pediatric patients

1. Initiate pharmacologic monotherapy with a non-FLV SSRI and titrate^a to the maximally tolerated dose for a minimum 10 week trial as per clinical judgement;
2. If an inadequate response is obtained, switch^b to FLV and titrate^a to the maximally tolerated dose for a minimum 10 week trial;
3. If an inadequate response is obtained, add CMI 25 mg PO daily and titrate upwards to the maximally tolerated dose for a minimum 10 week trial, keeping the combined CMI+DCMI level below 450 ng/mL. When the initial FLV monotherapy total daily dose exceeds 200 mg per day, consider decreasing FLV to 100-150 mg daily as CMI is increased to decrease risk of serotonin syndrome;
4. After each FLV and/or CMI dose adjustment, monitor serum CMI and DCMI concentrations and ECG/QTc interval^c after a minimum of 14 days.

^aGradually titrate the dose upward to the maximally tolerated dose (while OCD symptoms persist) while monitoring efficacy and potential adverse effects.

^bSSRI switching regimens may vary considerably, depending on a number of factors, including avoidance of serotonin overload/serotonin syndrome, avoidance of symptoms of SSRI discontinuation syndrome, while minimizing the duration the patient remains inadequately treated during the medication switch. Online resources such as www.switchRx.com may be of assistance in developing appropriate switching regimens.

^cIncreases in QTc interval >60 msec from baseline, or absolute QTc values >500 msec are used as typical thresholds for drug discontinuation (U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 2005). Patients with on-treatment QTc values between 450 msec and 500 msec may require discontinuation of further CMI dose titration and further ECG monitoring. For on-treatment QTc values above 500 msec, CMI dose reduction should be considered.

Consequently, the peak doses achieved do not necessarily correlate to the most effective doses.

Lastly, all identified patients were adolescents and it is unknown if the current findings are consistent in children under 12 years of age.

Clinical Significance

This is the first report of combination FLV+CMI therapy in pediatric patients with OCD. Combination FLV+CMI appears safe and well tolerated based upon this preliminary data. Knowledge of the safety of this combination is very important, given the limited pharmacologic options for severe, refractory OCD. Rational combination of FLV+CMI requires monitoring of serum concentrations of CMI and DCMI, ECGs, and clinical exam to assess for signs or symptoms of serotonin syndrome. Further study is needed to evaluate efficacy.

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Conflicts of Interest

The authors have no financial relationships to disclose.

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