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

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Background

- Obsessive-compulsive disorder (OCD) manifests as functional impairment due to obsessions, compulsions, or both
- Pediatric OCD severity is rated on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)
- Pharmacotherapy with serotonin reuptake inhibitors (SRIs) is reserved for moderate to severe presentations as an adjunct to cognitive behavioural therapy per American Academy of Child and Adolescent Psychiatry guidelines[1]
- Despite a smaller effect size than the second-line non-selective SRI clomipramine (CMI, a tricyclic antidepressant), selective SRIs (SSRIs; e.g. fluvoxamine, FLV) are recommended first-line due to safer adverse effect profiles
- SSRI augmentation with CMI, antipsychotics, or clonazepam may be used if adequate trials of SRI monotherapy fail
- CMI adverse effects are attributed to desmethylclomipramine (DCMI), an active, adrenergic metabolite formed via CYP1A2 (major), CYP2C19 (major) and CYP3A4 (minor), which are all inhibited by FLV
- Combination FLV and CMI (FLV+CMI) should therefore maximize the beneficial serotonergic effects of CMI and minimize the adverse adrenergic effects of DCMI
- A case series of 22 adults with OCD and depression demonstrated FLV+CMI safety when the [DCMI]:[CMI] ratio was ≤ 0.3 and the total serum concentration (CMI+DCMI) was ≤ 450 ng/mL[2]
- Data regarding efficacy and safety of FLV+CMI in pediatric patients with OCD is lacking

Objectives

- To characterize the pharmacokinetic interaction, dosing, and safety of FLV+CMI in pediatric patients with OCD
- To inform a dosing strategy for FLV+CMI in pediatric OCD

Methods

- **Design:** Retrospective chart review
- **Inclusion criteria:**
  - ≤18 years of age at initiation of FLV+CMI
  - Inpatients at BC Children's Hospital and outpatients under consultation with the Provincial Pediatric OCD Program
  - ≥1 measurement of CMI and DCMI serum concentrations
- **Study period:** January 1, 2010, to August 31, 2017
- **Analysis:** Descriptive statistics

Results

Table 1: Patient characteristics

	n=6
Age, years, median (range)	15 (14-18)
Female, %	50
Weight, kg, mean (SD)	52.5 (±10.6)
Number of prior SRI trials per patient, median (range)	2 (1-3)
Number of prior OCD augmentation trials per patient, median (range)	2 (0-3)

Figure 1: Semi-log plot of serum concentration ratio [DCMI]:[CMI] versus fluvoxamine dose (mg)

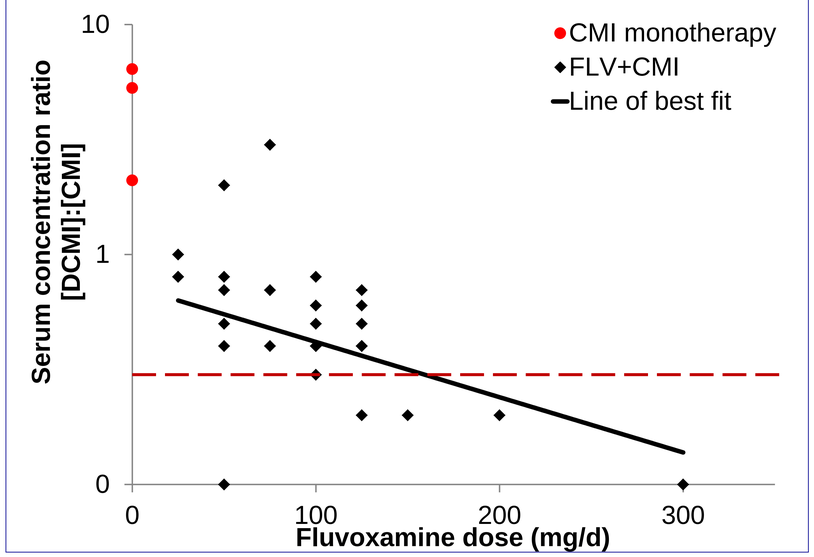


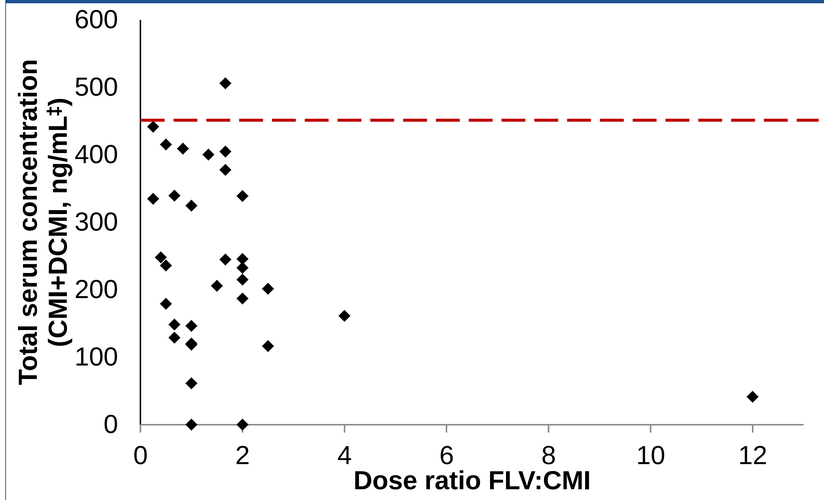
Table 2: SRI dosing and serum concentrations

	n=6
Peak CMI dose, mg/day, median (range)	87.5 (50-150)
Peak FLV dose, mg/day, median (range)	112.5 (25-300)
Dose ratio, FLV:CMI, median (range)	1.2 (0.3-12)
Total serum CMI+DCMI, ng/mL, median (range)	223.7 (0-505.9)
Ratio of DCMI:CMI, median (range)	0.4 (0-3)

Table 3: Safety outcomes

	n=6
Patients experiencing ≥ 1 adverse effect, n	3
Sedation, n	1
Fatigue, n	1
Dry mouth, n	1
Constipation, n	1
QTc > 450 ms, n	1

Figure 2: Total serum concentration of CMI+DCMI (ng/mL) versus dose ratio FLV:CMI



‡Non-SI units (ng/mL) used for interpretation and analysis based on Szegedi et al[2]

Limitations

- Retrospective design with small sample size
- No patients under 12 years of age identified
- Unable to verify medication adherence and consistency of timing of serum levels relative to last dose
- Unable to assess clinical efficacy as CY-BOCS inconsistently administered and/or documented
- Incomplete reporting of potential confounders (e.g. smoking for CYP1A2 induction) and adverse events
- Variable sequence of medication initiation

Conclusions

- FLV appears to inhibit DCMI formation in a dose-dependent manner
- Studied patients needed FLV doses ≥100 mg/day to adequately inhibit DCMI formation
- Inter-patient variability suggests therapeutic drug monitoring of CMI and DCMI serum concentrations required to assess CYP inhibition
- One patient demonstrated saturable CMI pharmacokinetics
- FLV+CMI generally well tolerated
- Further study needed to evaluate efficacy

References

1. Geller DA, March J; AACAP Committee on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2012;51(1):98 –113.

2. Szegedi A, Wetzel H, Leal M, et al. Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety, and tolerability data. J Clin Psychiatry. 1996;57:257-64.