

Interest of Fluvoxamine as an Add-on to Clozapine in Children With Severe Psychiatric Disorder According to CYPs Polymorphisms: Experience From a Case Series

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Case Report

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Abstract

Background

Despite its drastic efficacy in resistant psychiatric disorders, clozapine remains rarely used in youth due to its side effects. Clozapine plasma level is determined through its metabolism involving several isoforms of cytochromes 450 (CYP450) family. Isoform CYP1A2 appears as a limiting enzyme involved in the metabolism of clozapine while isoforms 2C19, 2D6, 3A4 and 3A5 also contribute in a minor way. Clozapine efficacy is limited by a significant inter-patient variability in exposure according to CYP's polymorphisms. Clozapine plasma levels may be increased with CYP inhibitors such as fluvoxamine. This drug is a potent enzymatic inhibitor of CYP1A2 and to a lesser extent of CYP3A4 and CYP2D6. Hence, in case of CYPs polymorphisms in youth, the use of fluvoxamine as add on to clozapine could help reaching clinical and biological efficacy and allowing lower clozapine dosage and a better tolerance profile, as it has already been described in adults.

Case Report

We report four pediatric cases with severe psychiatric disorders underlying our experience with CYPs polymorphism explorations and the use of fluvoxamine as add on to clozapine. Our four patients clinically improved after the introduction of fluvoxamine, enhancing clozapine metabolism and therefore clozapine plasma level within therapeutic range. Despite the interesting results of fluvoxamine, we report a severe issue of tolerance for one patient, emphasizing the need for caution regarding possible drugs interactions when fluvoxamine is considered. Hence, we propose a detailed step by step multidisciplinary protocol.

Conclusion

The results pointed out the positive clinical effects of fluvoxamine as add-on to clozapine in youth with severe neurodevelopmental disorders but stresses the need for caution regarding drugs interactions.

Background

In the last years, several studies in children and adolescents with severe psychiatric disorders have demonstrated the effectiveness and safety of clozapine. Clozapine is the gold standard for treating treatment-resistant adult patients with schizophrenia after at least two treatment failures (1, 2). For treatment-refractory early-onset schizophrenia (EOS), several studies show that clozapine is the most effective medication both in short-term and maintenance treatment (3–10). Clozapine also showed a better outcome for patients with schizophrenia secondary to 22q11 deletion. Indeed there is a higher prevalence of first-line antipsychotic resistance for those patients (11–13). Data in pediatric population are really sparse, and limited to case reports. Clozapine could be also useful for resistant pediatric bipolar disorder (14–16). Several studies have demonstrated the efficacy of clozapine in children and adolescents with aggressive behaviors in psychotic disorders (17, 18) or disruptive disorder (19, 20). Retrospective studies, case series and case reports, suggest efficacy of clozapine for aggressive behavior in autism spectrum disorder (ASD) or other pervasive developmental disorder (PDD) (21–27). To date, there is no randomized controlled study evaluating this use. Finally, evidence suggesting the efficacy of clozapine in Tourette's Syndrome is limited and heterogeneous (28–32).

Despite its high efficacy, *The American Academy of Child and Adolescent Psychiatry* (33) recommends the use of clozapine only after the failure of two or three other antipsychotics in EOS because of its significant side-effect profile. Clozapine is an atypical antipsychotic with a complex pharmacological profile: a higher affinity for 5-HT_{2A} receptors than D₂ and a lower occupancy D₂ compared to other antipsychotic drugs. Whereas, it results in less extrapyramidal effect, tardive dyskinesia and hyperprolactinemia, it has significant clinical risks such as agranulocytosis, seizures, myocarditis, or cardiometabolic adverse events regardless of the population adult or pediatric (34, 35). Moreover, children and

adolescents treated with clozapine or other antipsychotics have significantly higher adverse effects like weight gain than the adult population (36). Women and children have higher plasma levels than men and older people (37, 38) and it is likely that these higher levels could increase the rate of adverse events in these populations.

Clozapine plasma level is determined through its metabolism involving hepatic function, several cytochromes (CYP) and the Flavin-containing monooxygenase 3 (FMO3). In the liver, clozapine is mainly demethylated to N-desmethylclozapine (abbreviated NDMC, also called norclozapine) and oxidated to clozapine-N-oxide by several isoforms of CYP450 family. First, isoform CYP1A2 appears as a limiting enzyme involved in the formation of NDMC while isoforms 2C19, 2D6, 3A4 and 3A5 also contribute in a minor way. Isoforms CYP1A2, 2C19, 3A4 and 3A5 highly contribute to the metabolism of clozapine into clozapine N-oxide, while CYP2C9, CYP2D6 and FMO3 are involved to a lesser extent. N-desmethylclozapine is an active metabolite acting as a D2, D3 partial agonist (39), and having affinity for muscarinic, serotonin and histaminic receptor (40). Overall, clozapine's metabolism mainly involves CYP3A4 CYP1A2, CYP2C19 and FMO3, respectively for 70%, 5% 15% and 5% (41). Clozapine use is limited by a narrow therapeutic range and significant inter-patient variability in exposure according to CYP's polymorphisms. Genetic polymorphisms in the CYP450 genes are thought to account for about 50% of the clozapine plasma level. The remaining fifty percent mainly depends on the posology, gender and age (42, 43).

Clozapine plasma levels may also vary according to concomitant treatments such as CYP inhibitors including fluvoxamine. Fluvoxamine is a selective serotonin reuptake inhibitor and a sigma-1 receptor agonist (44). This drug is also a potent enzymatic inhibitor of CYP1A2 and to a lesser extent of CYP3A4 and CYP2D6. This inhibition activity is effective for a dosage of 50 mg daily in adults (45). Adjunction of fluvoxamine is associated with an increase in Clozapine-to-NDMC ratio and a lower NDMC plasma level by inhibiting CYP1A2 (46). Clozapine plasma level is increased by 2 to 10 with 50 mg/d of fluvoxamine, according to a wide interindividual variability of this effect (47). Associating fluvoxamine to clozapine leads to an improvement of metabolic parameters with a decrease in weight gain, insulin resistance and triglyceride levels (48). Clozapine-to-NDMC ratio has been previously shown to be a better indicator of clinical response than clozapine plasma level in pediatric population (7). The optimal ratio has not been defined yet, however a ratio of 2 seems to be associated with a maximal clinical efficacy (46). Hence the use of fluvoxamine as add on to clozapine is thought to help reaching efficacy with lower clozapine dosage and a better tolerance profile (46). Consequently, fluvoxamine is widely used in adults to optimize clozapine exposure and to reduce frequent side effects. To the best of our knowledge, to date, only one case report was published in a 16-years old boy with severe side effects, disturbing treatment maintenance. We report our experience with the use of fluvoxamine in four severely ill children who required the introduction of clozapine as a monotherapy at first, but quickly enhanced by addition of fluvoxamine.

A protocol pattern specific to our unit (with a slower increase than in adults) was used for the introduction and increase of clozapine dosing. Clozapine was initiated at a daily dose of 12.5 mg at night on day 1, 25 mg at night on day 2 and then dosing was increased by step of 25 mg every 3 days distributed as follow: lower dosing at morning and higher dosing at night, with difference of 25 mg to 100 mg between the two dosing (ie; BID: 100 mg at morning and 150 mg at night). Clozapine and N-desmethylclozapine plasma levels, complete blood count (CBC) and electrocardiogram (ECG) were monitored weekly. The targeted clozapine plasma level was 350 ng/mL (49). If clozapine plasma level was under 350 ng/mL, we searched for all possible causes of low clozapine plasma level such as poor compliance, inflammatory syndrome, medication interaction or alimentary interaction (49). After eliminated these causes, we performed pharmacogenetics testing for CYP. In case of identification of a clinically-significant polymorphism known as causal for low clozapine plasma level we introduced fluvoxamine as add on to clozapine after a multidisciplinary concertation with pharmacology department.

All families provided a written informed consent to the use of clozapine for their children, after being fully informed of: i) the off-label use and its scientific rationale in the matter of resistant neurodevelopmental disorders; ii) the clinical requirements and criterions for being considered as having a resistant psychiatric disorders iii) the clinical

pharmacokinetics of clozapine; iv) all possible side effects and contraindications known with clozapine and v) the specific side effects monitoring scheduled. All families provided a written informed consent for CYP genotyping. In addition, all families provided a written informed consent to the use of fluvoxamine for their children, after being fully informed of: i) the off-label use and its scientific rationale in the matter of increasing CYP metabolism in a context of identified polymorphism ; ii) all possible side effects and contraindications known with fluvoxamine and iii) the specific side effect monitoring scheduled. No family or legal guardian refused the offer of both treatment or CYP genotyping. This study E2020-85 was approved by our Ethical committee for research on preexisting data at the University Teaching Hospital of Rouen. The committee concluded that this study do not present any ethical issue and any violation of “Loi n° 2012 – 300 du 5 mars 2012 (dite loi Jarde) ”. This study is consistent with and conforms to French Law regarding clinical research.

Case Report 1

A is an 11-year-old caucasian girl, born at term after a complicated pregnancy and a threat of preterm birth during the fifth month in a context of physical violence towards her mother. No complication was reported during the delivery. She was eutrophic at birth. APGAR score was 10/10. She suffers from a permanent moderate hyperphenylalaninemia diagnosed at birth. A diet alone led to acceptable phenylalaninemia levels. This condition severely limits drugs options, due to the contraindication of aspartame. Regarding psychomotor development, no delay was found during her first year.

She was placed in foster care at the age of six due to severe neglected behaviors from her parents. She has experienced a very insecure environment leading to an early attachment disorder and anxiety disorder. During primary school, major global learning disabilities were reported. In this context, she was evaluated by a standard metric test (EXALANG 5–8 years). The initial evaluation found severe attentional and behavioral difficulties leading to poor reading and writing skills. Writing rehabilitation was prescribed but stopped due to behavioral disorders. At the age of nine, the Wechsler Intelligence Scale for Children (WISC–IV) was homogeneous with intellectual disability (Verbal Comprehension Index = 69; Perceptual Reasoning Index = 82; Processing Speed Index = 71; Full Scale IQ = 69). Rapidly, she presented severe outbursts and tantrums leading to hetero-aggressiveness and self-injuries. In the meantime, she started to exhibit many simple motor tics associated with simple verbal tics characterized by facial grimacing, arms jerk, obscene gesture and scream compatible with a Tourette syndrome. The worsening of Tourette syndrome associated with intellectual deficiency led to many changes in her living environment and many long-term hospitalizations. She was unsuccessfully challenged by : risperidone, aripiprazole, fluoxetine, propericiazine, haloperidol, zuclopenthixol and naltrexone.

During her last admission in our specialized unit, our clinical assessment underlined the severity of her attachment disorder with severe ambivalence towards her relationship with peers and caregivers, many simple and complex motor/verbal tics, aggressiveness, strong impulsivity and numerous self-harm behaviors. Given the overall resistance to atypical and typical antipsychotics, the severity and burden of the automutilations and impulsivity, the off-label use of clozapine was considered legitimate by the medical team. We quickly reported low clozapine plasma levels (275 ng/mL), regardless of the progressive increase of clozapine dosage (500 mg/d). Pharmacogenetics testing on cytochromes was performed and identified *CYP1A2*1F/*1F* genotype (**See Table 1**). This genotype is associated with ultra-rapid drug metabolism, therefore explaining the low clozapine plasma levels. We decided to add fluvoxamine to clozapine, to inhibit the CYP1A2 subunit and to enhance clozapine plasma level. Within the next days after fluvoxamine introduction (50 mg/d), we observed a major increase of clozapine plasma level (503 ng/mL) (**See Fig. 1**). Clinically, we reported a drastic improvement regarding automutilations and impulsivity with a 32% reduction in the ABC-Irritability subscale and 33.3% in the ABC-Hyperactivity subscale. Tolerance was excellence and no hematological adverse was reported (**See Additional files 1**).

Case Report 2

B is a 9-years-old african boy, born at term after a normal pregnancy. He was placed in foster care at the age of three due to severe physical and psychological violences within the family and severe neglected cares. He barely had contact with his mother and his father. His family background is marked with a psychotic disorder in one first degree relative. He quickly presented a delay in language and motor skills. An Ears, Nose, and Throat (ENT) exploration and audiometry were performed at the age of four without any abnormalities. He did not receive speech therapy or psychomotor therapy. Academic performances were severely impaired due to his global and severe neurodevelopmental delay. School was quickly impossible and interrupted, due to repetitive admission in psychiatry for tantrums and severe outbursts. Around the age of eight, B presented an increase of behavioral disorders occurring at school and at home, leading to several hospitalizations for severe outbursts, self-harm and aggressive behaviors. At the same time, he reported a progressive onset of visual and auditory hallucinations. Risperidone was initiated at 2 mg/d without any efficacy.

At the admission in our unit, B presented delusional ideas, hallucinations and mental automatism. He exhibited a disorganized and dissociative motor behavior, disorganized processes of thinking with speech disorder and cognitive impairment. After an extensive screening panel (**See Additional files 2 for details of screening panel**), no organic cause was retrieved and the diagnosis of EOS was retained. Aripiprazole was introduced at 15 mg/d associated with levomepromazine at 15 mg/d. However, patient's tolerance was questioned with a severe sedation and a worsening of delusions and hallucinations. Aripiprazole plasma level showed an overdose at 835 ng/mL (therapeutic reference range: 150–500 ng/mL) regardless of the proper dosage-weight ratio. Aripiprazole was then switched to haloperidol, gradually up to 1.5 mg/d. There was no improvement regarding positive symptoms. Haloperidol and levomepromazine plasma level found an underdose respectively at 1.1 ng/mL and 5 ng/mL Hence, a heterogenous genotype CYP metabolism was suspected. Pharmacogenetic testing for cytochromes was performed and identified *CYP2D6*1/*10* and *CYP2D6*1/*41* heterozygous genotypes and a *CYP3A5*1/*1* homozygous genotype (**See Table 1**). These genotypes are associated with a partial deficiency in CYP2D6 activity and a ultra-rapid metabolizer phenotype CYP3A5, respectively. Therefore these genotypes are genetic explanations of the high aripiprazole plasma level and low haloperidol plasma level. Given the resistance to two atypical antipsychotics and one typical antipsychotic, the severity and burden of the psychotic features, the off-label use of clozapine was legitimate. However, during progressive increase of clozapine dosage (300 mg/d), we reported a low clozapine plasma level (124 ng/mL). After a multidisciplinary staff, we decided to add-on fluvoxamine to clozapine. Few days after fluvoxamine's introduction (50 mg/d), the patient presented an extreme sedation and QTc prolongation requiring a transfer to the pediatric cardiology department for continuous monitoring and discontinuation of drugs. Indeed, a relatively high levomepromazine plasma level (140 ng/mL, therapeutic reference range in adults: 5–25 ng/mL) was retrieved due to CYP2D6 inhibition by fluvoxamine. Clozapine plasma level was low (139 ng/mL). Therefore, the extreme sedation was secondary to an overdose of levomepromazine, leading to discontinuation of the drug. Clozapine was introduced once again in association with low dose of fluvoxamine (25 mg/d). Within the next days after fluvoxamine introduction, plasma clozapine level dramatically increased (**See Fig. 1**) associated with a important improvement of the clinical state regarding positive symptoms (66% reduction in the SAPS) and a reduction of aggressive behavior. Tolerance was good without, among others, blood count abnormalities (**See Additional files 1**).

Case Report 3

C is a 14-year-old adolescent (caucasian/indian ancestry), born at term by caesarean section due to foetal bradycardia. He is the only son of divorced parents. His family history includes a depressive disorder in two first and second-degree relatives and a psychotic disorder in a second-degree relative. He presented language delay secondary. He subsequently received speech therapy. C exhibited significant learning delays, particularly in terms of graphical skills with dyspraxia, difficulties in attention, memory and processing instructions. He also received psychomotor rehabilitation. He went through a standard academic course until secondary school. However, he quickly showed significant absenteeism and dropped out of school due to his psychiatric symptomatology.

His psychiatric follow-up started at the age of three years old due to his difficulties in interacting with his peers and social withdrawal. A diagnosis of ASD was made when he was twelve. At the age of thirteen, C was hospitalized at the request of his psychiatrist when negative and positive symptoms appeared. Aripiprazole 10 mg/d was initiated at that time, but C promptly stopped treatment upon discharge from the hospital. A few months later, he presented significant disturbances in the processes of thinking as well as mystical and persecution delusions. After the admission to our unit, C exhibited negative symptoms with apragmatism, social withdrawal and marked emotional blunting. The positive symptoms were sub-acute and mild but C was reluctant to express them due to egosyntonia. After an extensive screening panel (**See Additional files 2 for details of screening panel**), no organic causes was identified and the diagnosis of EOS was retained with a probable pre-morbid ASD condition. Amisulpride was then initiated. However, one week after the introduction, he presented asymptomatic hyperprolactinemia (80 ng/mL, therapeutic reference range: < 15 ng/mL), requiring the discontinuation of amisulpride. Prolactin levels were normalized within one month after the intervention. A new introduction of aripiprazole at 15 mg/d allowed a regression of delusions and hallucinations, with a good tolerance. After discharge from hospital, C benefited from a neurocognitive rehabilitation program and adolescent daycare clinic. After six months, he exhibited a progressive increase of delusions and hallucinations leading to a switch from aripiprazole to haloperidol 1.5 mg/d. At that point, C was admitted again in our unit. He reported a poor therapeutic compliance leading to a worsening of delusions (mystical, filiation, persecution) and cenesthetic hallucinations with a total adherence. Given the EOS resistant to two atypical antipsychotics and one typical antipsychotic, the severity and burden of the psychotic features, the off-label use of clozapine was legitimate. However we reported fluctuating low clozapine plasma levels (from 248 to 407 ng/mL) with clozapine dosage between 400 and 500 mg/d, and a total lack of clinical response. A pharmacogenetic testing on cytochromes was performed and identified a *CYP2C9*1/*3* heterozygous genotype (**See Table 1**). This genotype is associated with a decreased CYP2C9 activity that could partially explain the low clozapine plasma levels. Giving the major lack of clinical response and other possible unidentified polymorphisms associated to *CYP2C9*1/*3* heterozygous genotype, we decided to add-on fluvoxamine to clozapine. Five days after fluvoxamine introduction (starting at 25 mg/d to 50 mg/d), a first increase in clozapine plasma level (467 ng/mL) was observed (**See Fig. 1**). Clinically, we underlined a drastic improvement regarding positive symptoms with a 63.3% reduction in the SAPS. Tolerance was excellence and no hematological adverse was reported (**See Additional files 1**).

Case Report 4

D is an 11-years-old caucasian boy, who was born at term after a normal pregnancy. He was diagnosed with a mild ASD at the age of eight. Genetic testing (fragile X syndrome, karyotyping, CGH array), metabolic panel and ENT exploration were negative. His family background is marked by intellectual disability in one-second degree relative. He is living with his parents and his brother. Autonomy was partial and communication skills were characterized by several simple words and short answers to questions.

In January 2019, parents described a sudden and brutal increase of abnormal movements, including turning on itself, grimacing and new stereotypies. He also exhibited sudden behavioral changes, became aggressive, withdrawn and anxious. He started to speak less, presented enuresis and a refusal to eat with a loss of weight and slept poorly. These behavioral changes led to school drop out. Several stress factors during this period has occurred in the last months: moved to a new house four months before, suspicion of bullied stress at school and hand-foot-mouth disease two months before. Risperidone and fluoxetine were introduced but without any efficacy.

He was admitted in our unit on July 2019 for mixed catatonia with psychomotor agitation, stereotypes, automatic compulsive movements, grimacing, posturing and negativism. We reported waxy flexibility, catalepsy and echolalia at the clinical examination. Pediatric Catatonia Rating Scale (PCRS) score was 29. We slowly increased lorazepam to 16.5 mg/d, allowing stabilizing the catatonic syndrome (PCRS score at 10). An extensive screening panel was performed (**See Additional files 2 for details of screening panel**). No abnormalities were found. However, there was a persistence of

aggressive behaviors, screaming and crying associated with significant anxiety. Aripiprazole 2.5 mg/d was introduced. Prazosin was also introduced because of the suspicion of a post-traumatic disorder and the presence of repetitive nightmares and sleep disturbance. He presented no adverse event. After three months of hospitalization, catatonia and general anxiety disorder were stabilized with a PCRS score at 2, allowing a discharge with 13.5 mg/d of lorazepam. However, after returning home, he still refused to go to school or leave the house. He did not want to be apart from his mother and refused to let people go home. He presented a loss of interest, withdrawal and aggressive behavior. A month later he was admitted again.

Given the resistance to two atypical antipsychotics, the severity and burden of anxiety and aggressive behavior, the off label use of clozapine was legitimate. However, during this progressive increase of clozapine dosage (200 mg/d), the clozapine plasma level did not reach the therapeutic range (< 50 ng/mL). A pharmacogenetic testing on cytochromes was performed and identified a *CYP1A2**1/*1*F* heterozygous genotype, a *CYP2D6**1/*4 and *CYP2D6**1/*10 heterozygous genotype and a *CYP2C19**1/*2 heterozygous genotype (See Table 1). These genotypes are associated with an ultra-rapid drug metabolism, therefore explaining the low clozapine plasma level. These polymorphisms can also explain the lack of improvement of previous treatments. We decided to add fluvoxamine to clozapine. One days after fluvoxamine introduction (starting at 25 mg/d to 50 mg/d), a drastic increase in clozapine plasma level (261 ng/mL) was observed (See Fig. 1). Clinically, we underlined a drastic improvement regarding aggressive behavior with a 100% reduction in the ABC-Irritability subscale and 90% in the ABC-Hyperactivity subscale. Tolerance was excellent, repeat blood sample was not a reason to stop treatment and no hematological adverse was report (See Additional files 1).

Table 1
Pharmacogenetics testing for cytochrome

	CASE 1	CASE 2	CASE 3	CASE 4
GENOTYPE CYP1A2	<i>CYP1A2*1F/*1F</i>	<i>CYP1A2*1/*1</i>	<i>CYP1A2*1/*1</i>	<i>CYP1A2*1/*1F</i>
GENOTYPE CYP2D6	<i>CYP2D6*1/*1</i>	<i>CYP2D6*1/*10</i> <i>CYP2D6*1/*41</i>	<i>CYP2D6*1/*1</i>	<i>CYP2D6*1/*4</i> <i>CYP2D6*1/*10</i>
GENOTYPE CYP2C19	<i>CYP2C19*1/*1</i>	<i>CYP2C19*1/*1</i>	<i>CYP2C19*1/*1</i>	<i>CYP2C19*1/*2</i>
GENOTYPE CYP3A5	NA	<i>CYP3A5*1/*1</i>	<i>CYP3A5*3/*3</i>	<i>CYP3A5*3/*3</i>
GENOTYPE CYP3A4	<i>CYP3A4*1/*1</i>	<i>CYP3A4*1/*1</i>	<i>CYP3A4*1/*1</i>	<i>CYP3A4*1/*1</i>
GENOTYPE CYP2C9	NA	NA	<i>CYP2C9*1/*3</i>	<i>CYP2C9*1/*1</i>
Predicted phenotype	CYP1A2 : ultra rapid metabolizer CYP2D6 : extensive metabolizer CYP2C19 : Extensive or rapid metabolizer CYP3A5 : NA CYP3A4 : Extensive or rapid metabolizer CYP2C9 : NA	CYP1A2 : extensive metabolizer CYP2D6 : intermediate metabolizer CYP2C19 : Extensive or rapid metabolizer CYP3A5 : ultra rapid metabolizer CYP3A4 : Extensive or rapid metabolizer CYP2C9 : NA	CYP1A2 : extensive metabolizer CYP2D6 : extensive metabolizer CYP2C19 : Extensive or rapid metabolizer CYP3A5 : slow metabolizer CYP3A4 : Extensive or rapid metabolizer CYP2C9 : intermediate to slow metabolizer	CYP1A2 : ultra rapid metabolizer CYP2D6 : intermediate to slow metabolizer CYP2C19 : intermediate to slow metabolizer CYP3A5 : slow metabolizer CYP3A4 : Extensive or rapid metabolizer CYP2C9 : Extensive or rapid metabolizer

NA : Not available ; CYP : Cytochrome

All demographics and clinicals characteristics of each patient are summarized in Table 2.

Table 2
Demographics, diagnosis, clinical response and treatments.

	CASE 1	CASE 2	CASE 3	CASE 4
Sex	Female	Male	Male	Male
Age (Years)	11	9	14	10
BMI (Kg/m2)	15	23	16,6	14,2
Ethnic origin	Caucasian	African	Caucasian / Indian	Caucasian
Diagnosis (DSM-V)	Tourette Syndrome PDD	EOS	EOS	ASD
Clinical response	Positive response on irritability hyperactivity and aggressive behavior	Drastic response on hallucinations and delusions	Drastic response on hallucinations and delusions	Positive response on irritability hyperactivity and aggressive behavior
Mean scores difference of clinical scales (ABC, SAPS)	ABC scores: Δ Irritability : 32% Δ Hyperactivity: 33,3%	SAPS Δ : 66%	SAPS Δ : 66,3%	ABC scores Δ Irritability: 100% Δ Hyperactivity: 90%
Prior Psychotropic treatments	Risperidone Aripiprazole Fluoxetine Propericiazine Haloperidol Zuclophenithoxol Naltrexone	Risperidone Aripiprazole Haloperidol	Aripiprazole Amisulpride Methylphenidate Haloperidol	Risperidone Fluoxetine Aripiprazole
Treatments maintained during fluvoxamine introduction	Clozapine Pimozide Lorazepam	Clozapine	Clozapine	Clozapine Prazosine Nefopam Lorazepam

ABC: Aberrant Behavior Checklist; ASD: Autism Spectrum Disorder; BMI : Body Mass Index ; DSM-V : The Diagnostic and Statistical Manual of Mental Disorders -V ; EOS : Early-Onset Schizophrenia; PDD : Pervasive Developmental Disorder ; SAPS: The Scale for the Assessment of Positive Symptom

Discussion

To our knowledge, this case series is the first detailed report of pediatric use of fluvoxamine to enhance clozapine. Our four patients clinically improved after the introduction of fluvoxamine as add on to clozapine, enhancing its metabolism and therefore plasma level within clozapine's concentration therapeutic range. Tolerance was good except for the case 2. However this could be attributed to a drug-drug interaction, since it did not occur when the combination fluvoxamine and clozapine was introduced again. It is important to stress that all our patients presented severe and resistant psychiatric disorders (EOS, ASD and PDD/Tourette syndrome), which justified the initial use of clozapine. It is clear that those patients

already represented a therapeutic challenge, as their psychiatric features could not be improved after several therapeutic options. Furthermore, those patients had initially shown no sign of improvement since the introduction of clozapine, with extremely low or negative plasma levels. We would like to discuss three main points: 1) the specifics of the interesting use of clozapine in severe pediatric psychiatric disorders, 2) the importance of exploring CYPs polymorphisms profile in severe psychiatric patients and 3) the encouraging use of fluvoxamine for a customized management of clozapine.

Among the severe psychiatric disorders supporting clozapine, early-onset schizophrenia (EOS) is a rare form of schizophrenia defined by an onset before the age of 18 with a prevalence < 1/10 000 children in the general population (50). Two systematic reviews of the literature (5, 6), have shown the superior efficacy of clozapine in resistant EOS. Clozapine improves all EOS features, including negative symptoms (7, 9) allowing a reduction in the number and period of hospitalizations (5). In our study, clozapine combined with fluvoxamine reduced SAPS score in case report 2 and 3, respectively by 66% and 66,3%, showing therapeutic response. Aggressive behavior is a significant concern with a major burden on the quality of life for patients with ASD and their caregivers. A retrospective review of 135 individuals with ASD demonstrated that 39.5% (n = 53) of individuals met criteria for drug refractory behaviors (defined by trials of risperidone and aripiprazole or three or more psychotropic drugs targeting irritability) (51). Clozapine has received very little attention, despite open label studies suggesting its potential efficacy on aggressive behavior in ASD (21–24, 52) and ID (27, 53). In our study, clozapine improved the ABC-Irritability sub-scores by 32% in case report 1 (severe neurodevelopmental disorder), and 100 % in case report 4 (ASD). Despite its drastic efficacy, clozapine remains rarely used in youth due to its side effects, particularly hematologic toxicity with the risk of agranulocytosis. The risk associated with clozapine can be minimized and better apprehended with a careful and close monitoring in severely ill youth who present psychotic symptoms resistant to conventional treatments (54). Among the four studied patients, clozapine was well tolerated, excepted in case report 2 according to a pre-existing drug-drug interaction involving levomepromazine that was corrected afterwards. None of the four patients had agranulocytosis, myocarditis or seizures, even after the add-on of fluvoxamine (See Additional files 1).

Several CYP450 enzymes are involved in clozapine metabolism. Clozapine pharmacokinetics may vary according to several functional single nucleotide polymorphisms (SNPs). There is a growing interest in the area of pharmacogenomics, but the prevalence of these SNPs is usually studied in adults. To date and to the best of our knowledge, data dealing with pharmacogenetics of antipsychotics in the pediatric population are lacking. Hepatic metabolism of clozapine is complex and involve several enzymes (49, 55, 56). Of these, CYP1A2 isoform plays a major role and the allele *CYP1A2*1F* (rs762551) is associated with an ultra rapid metabolism of substrates including clozapine and olanzapine (57). Ultra rapid metabolism may increase drug clearance and lead to low plasma levels of various treatments such as clozapine, inciting clinicians to conclude falsly about treatment inefficiency. Some authors found a prevalence around 51.3% for this genotype (58). Clozapine is also metabolized in a same manner by CYP3A4 and CYP2C19. CYP3A4 polymorphism exhibits considerable interethnic variability and *CYP3A4*22* (rs35599367) appears as the main deleterious SNP in Caucasians(54). CYP2C19 isoform is also highly polymorphic and *CYP2C19*2* (rs4244285) leads to a reduced metabolic activity while *CYP2C19*17* (rs12248560) is the main variant associated with an increased activity of this enzyme. To a lesser extent, CYP2D6 and CYP2C9 isoforms have been involved in the metabolism of clozapine. An increased activity of CYP2D6 is described in 0.7–5.6% of the caucasians (CYP2D6 copy number variation, i.e *CYP2D6*xN*) while about 30% are carrying deleterious allele(s) associated to a reduced CYP2D6 activity (59). These deleterious variants mailnly include *CYP2D6*3* (rs35742686), *CYP2D6*4* (rs3892097), *CYP2D6*5* (CNV, gene deletion), *CYP2D6*6* (rs5030655), *CYP2D6*9* (rs5030656), *CYP2D6*10* (rs1065852) and *CYP2D6*41* (rs28371725). Regarding the CYP2C9 isoform, *CYP2C9*2* (rs1799853), *CYP2C9*3* (rs1057910) are the main deleterious variants found in Caucasians. Moreover clozapine and its metabolites have been described as substrates of the highly polymorphic P-glycoprotein (P-gp) (*MDR1*) drug efflux transporters. However, the effects of P-gp variants on clozapine pharmacokinetics and pharmacodynamics remain unclear (55). In the present case series, two patients exhibited CYP1A2 ultra-rapid metabolizer genotype for clozapine. One other case presented an atypical metabolism profile based on the extremely low clozapine plasma level while none

mutations were found. Finally, case n°3 illustrates a limit of such targeted pharmacogenetic approach as no well-characterized polymorphism could explain the low clozapine plasma levels. In this specific situation, the decision of adding fluvoxamine was supported by: i) the absence of all other possible etiology (toxic, diet, drugs) which could have enhance CYP450, ii) the persistence of no clinical response to clozapine, iii) the persistence of undetectable clozapine plasma level, iv) the crucial need to improve psychotic symptoms and v) the fact that the absence of well-known mutations does not exclude other possible mutations not yet identified. This case raised two questions: firstly, for which clinical situation should we proceed CYP genotyping? – and secondly, when should we consider the addition of fluvoxamine to clozapine therapy?

Clozapine plasma level should be weekly monitored and reach a threshold of 350 ng/mL in order to expect efficacy (49). However, as discussed above, CYP450 polymorphisms can result in low plasma level and ineffectiveness of clozapine. Genotyping should be considered when persistent low (under 350 ng/mL) or negative clozapine plasma levels occur in regards of proper dosage (300 to 600 mg/d, from our clinical expertise); and when patients do not exhibit any clinical response and improvement. If both situations are present, fluvoxamine adjunction should seriously be considered (**See Fig. 2**). The add-on of fluvoxamine to clozapine increases clozapine plasma level and clozapine/norclozapine ratio by inhibiting cytochromes(46). This lead to increase therapeutic effect and reduce adverse effect and with lower dosage(46, 48). Our four patients showed a drastic increase of clozapine plasma level and ratio clozapine/ desmethylclozapine plasma level quickly after the introduction of fluvoxamine 25 mg (**See Fig. 1**).

Based on our clinical experience and the tolerance issue we faced in case 2, starting fluvoxamine at 50 mg/d following the same pattern than in adult population appeared unsuitable and unsafe for pediatric population with a risk of high increase of clozapine plasma level. Therefore, we reviewed our practice after concertation with the pharmacology department in our institution and proposed a strict protocol for the introduction of fluvoxamine as add on to clozapine in pediatric patients: 1) drugs interactions with fluvoxamine must be carefully assessed in order to identify all possible risk of overdosage of any on-going comedication other than clozapine ; 2) clozapine regimen should was adjusted at 200 mg/d in two separate take (100 mg in the morning and 100 mg in the evening), regardless of the previous dosage ; 3) systematically start fluvoxamine 25 mg/d (half the dosage used for adults) in order to better control the increase of clozapine plasma levels ; 4) therapeutic drug monitoring of clozapine plasma levels was systematic with CBC, and ECG monitoring twice a week; and 5) still targeting clozapine plasma through levels at 350 ng/mL. If this target is not achieved, we recommended to increase fluvoxamine regimen at 50 mg/d. If the clozapine plasma level remained systematically under 350 ng/mL after two weeks, we proposed to increase clozapine dosage with the same pattern described above. This protocol is summarized with an algorithm in Fig. 2.

However, the presented results should be interpreted in the context of several limitations. First, the number of case was low. Second, the absence of double blind use of fluvoxamine doesn't allow any validation of its safety in youth. The strengths of this case series must be underlined. This is the first report of fluvoxamine's use in pediatric population. To our knowledge, no other study took interest on the key role of CYP450 polymorphisms and fluvoxamine in order to better target treatment options for severe psychiatric disorders in youth. Despite the interesting results of fluvoxamine, we report a severe issue of tolerance for one patient (case report 2), emphasizing the need for caution regarding possible drugs interactions when fluvoxamine is considered. Hence, we propose a detailed protocol (**See Fig. 2**). Furthermore, we believe exploring CYP450 polymorphisms associated to a close therapeutic monitoring is an interesting clinical tool to better understand low response to drug or clinical resistance and to propose available therapeutic solutions such as fluvoxamine, besides the standard monitoring of treatment plasma levels. In the end, a close plasma level monitoring and adjunction of fluvoxamine could lead to a better understanding of clozapine efficacy, a targeted treatment approach, a shorter hospitalization, and less relapse in the future.

Conclusion

This case series underlines the benefits of clozapine in severe neurodevelopmental disorders. To our knowledge, this is the first study to report the importance of targetting CYP450 polymorphisms to explore clozapine pharmacokinetics and pharmacogenomics association and to guide toward a fluvoxamine add-on as a booster in pediatric population. The results pointed out the positive clinical effects of fluvoxamine as add-on to clozapine in youth with severe neurodevelopmental disorders. From our clinical experience, the use of fluvoxamine add on to clozapine in youths as it has already been described in adults appears usefull and interesting, but stresses the need for caution regarding drugs interactions and for future studies to validate its efficacy and safety on a larger sample .

Abbreviations

EOS: Early-Onset Schizophrenia ; ASD: Autism Spectrum Disorder ; PDD: Pervasive Developmental Disorder ; CYP: Cytochromes ; FMO3: Flavin-containing monooxygenase 3; NDMC: N-desmethylclozapine; CBC: Complete Blood Count ; ECG: electrocardiogram ; WISC: Wechsler Intelligence Scale for Children ; ENT: Ears, Nose, and Throat; ABC : *Aberrant Behavior Checklist* ; SAPS : Scale for the Assessment of Positive Symptoms; PCRS: Pediatric Catatonia Rating Scale ; SNPs: Single Nucleotide Polymorphisms; P-gp: P-glycoprotein

Declarations

Ethics approval and consent to participate: This study E2020-85 was approved by our Ethical committee for research on preexisting data at the University Teaching Hospital of Rouen. The committee concluded that this study do not present any ethical issue and any violation of “Loi n° 2012-300 du 5 mars 2012 (dite loi Jarde) ”. This study is consistent with and conforms to French Law regarding clinical research. A written consent to participate was signed by all the subjects involved and/or their parents.

Consent for publication: A written consent for publication was signed by all the subjects involved and/or their parents.

Availability of data and material: All relevant data are included in the article and/or its supplementary information files. All other data supporting the study are available from the corresponding author upon request.

Competing interest: Boris Chaumette has received speaking fees from Janssen-Cilag. Other authors have no conflicts of interest that might be relevant to the contents of this manuscript.

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Author Contributions : CB, UM and VF collected and processed the data and wrote the manuscript. JW, LC, LI, PG,BC, FL and VF reviewed the literature. CB and UM co-wrote the manuscript. All authors reviewed the manuscript.

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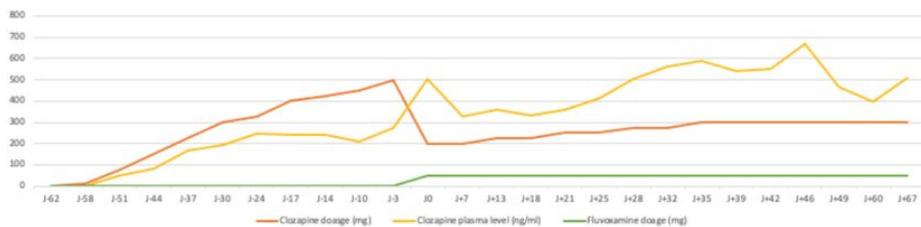
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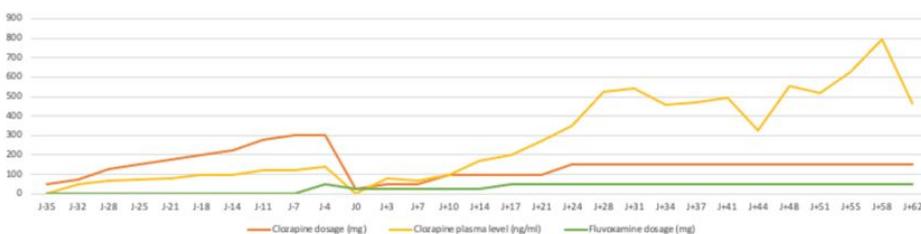
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Figures

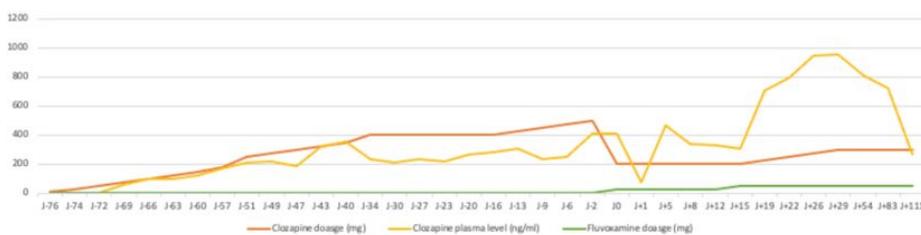
Case 1



Case 2



Case 3



Case 4

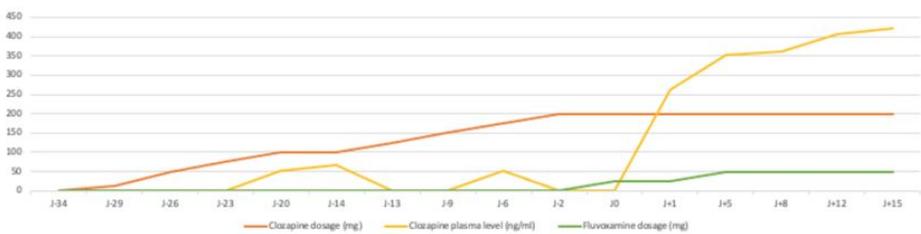


Figure 1

Evolution of clozapine plasma level (ng/ml) for each case J0 : Introduction of fluvoxamine.

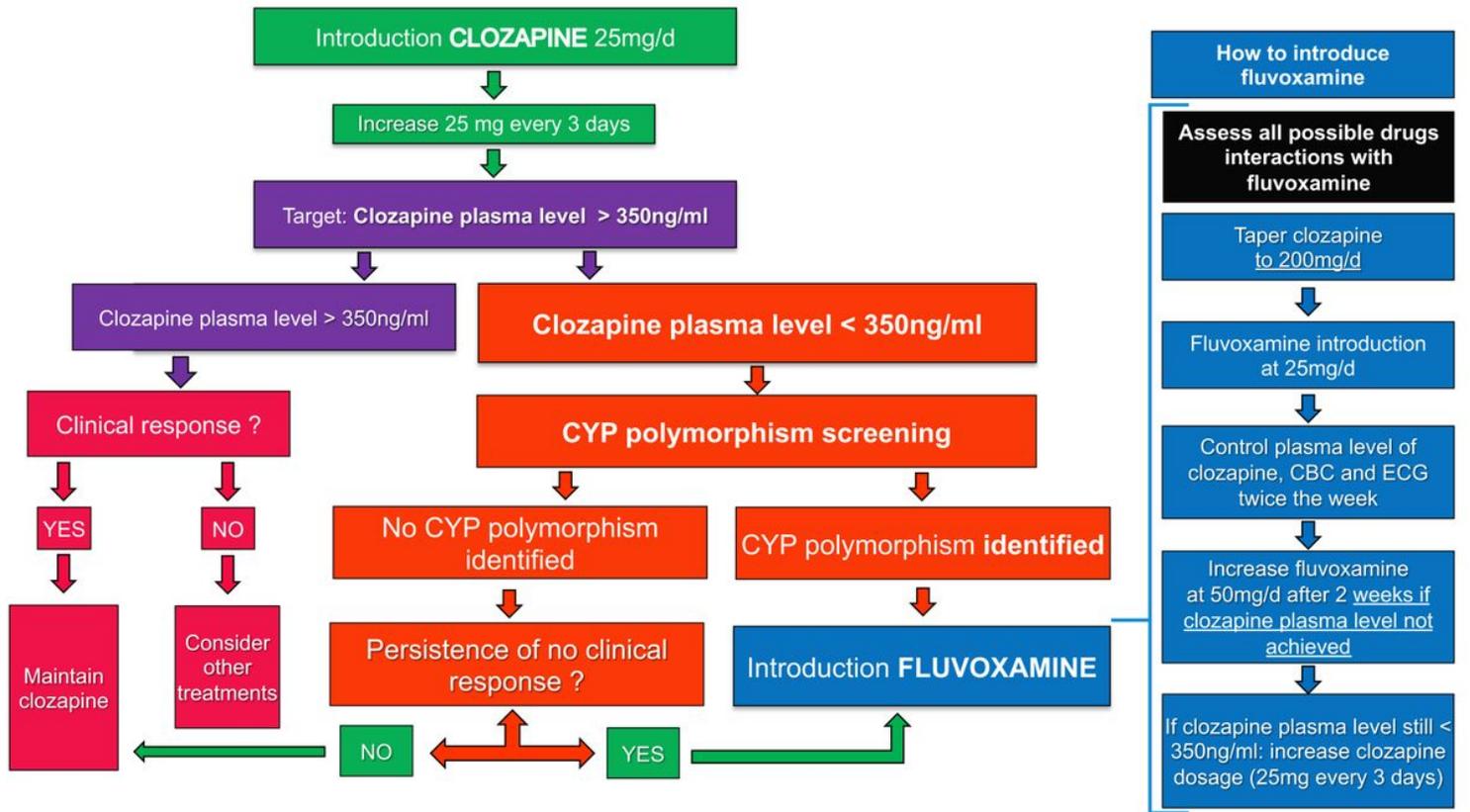


Figure 2

Organigram.

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