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Escitalopram Treatment in Preschool Children with Anxiety Disorders: A Case Series

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ÖZET:

Anksiyete bozukluğu olan okul öncesi çocuklarda essitalopram tedavisi: Bir olgu serisi

Amaç: Anksiyete bozukluğu olan okul öncesi çocukların tedavisinde essitalopramın etkinliği ve güvenilirliğine dair veri toplamak.

Yöntem: Bu çalışma anksiyete bozukluğu olan ve psikososyal girişim ve tedavilere cevap vermediği için essitalopram ile tedavi edilen okul öncesi çocukların tıbbi kayıtlarının geriye dönük incelemesidir. Hasta kayıtları olguların sosyodemografik özellikleri, DSM-IV tanıları ve essitalopram tedavisiyle ilişkili iyileşme ve yan etkiler açısından incelenmiştir. Semptom şiddeti ve iyileşme Klinik Global İzlem-Şiddet (KGİ-Ş) ve İyileşme (KGİ-İ) ölçekleri kullanılarak değerlendirildi.

Bulgular: Olgular 8 kız ve 3 erkek çocuktan oluşmaktaydı (yaş aralığı 47-64 ay; 55.45±5.90 ay). Maksimum essitalopram dozu 2-10 mg/gündü (3.72±2.49). Beş olgu obsesif kompulsif bozukluk semptomlarında KGİ-İ ölçeğinde hafiften çoğa değişen düzelme gösterdi. Üç olgu travma sonrası stress bozukluğu semptomlarında hafif, orta ya da oldukça düzelme gösterdi. Üç olgu diğer anksiyete semptomlarında orta ya da oldukça düzelme gösterdi. İki olgu (%18.18) her hangi bir yan etki bildirmedi. En sık bildirilen yan etki davranışsal disinhibisyon semptomlarıydı (n=5; 45.45%). 3 olguda (%27.27) tedavi yan etkilerden dolayı - başlıca davranışsal disinhibisyon semptomları- kesildi.

Sonuç: Anksiyete bozukluğu olan, belirgin bir işlev bozukluğu yaşayan ve/veya psikososyal girişimlere yanıt vermeyen okul öncesi çocuklarda essitalopram tedavide yardımcı olabilir. Okul öncesi çocuklar yan etki-özellikle davranışsal disinhibisyon semptomları-gelişmesi konusunda daha duyarlı olabilirler.

Anahtar sözcükler: Çocuklar, okul öncesi, anksiyete bozukluğu, essitalopram

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ABSTRACT:

Escitalopram treatment in preschool children with anxiety disorders: a case series

Objective: To provide data about the efficacy and tolerability of escitalopram treatment in preschool children with anxiety disorders.

Methods: This study is a retrospective chart review of preschool children with anxiety disorders treated with escitalopram. Medical records of the subjects were reviewed for sociodemographic features, DSM-IV diagnoses, improvement and treatment related side effects. Clinical-Global Impression-severity (CGI-S) and improvement (CGI-I) scales were used to assess symptom severity and improvement.

Results: The subjects were eight girls and three boys (age range 47 to 64 months; 55.45±5.90). Individual doses of escitalopram ranged between 2-10 mg/day (3.72±2.49). Five subjects showed mild to very much improvement in obsessive-compulsive symptoms on the CGI-I scale. Three subjects showed moderate to much improvement in anxiety symptoms and three subjects showed mild to much improvement in post-traumatic symptoms. Two subjects (18.18%) did not report any side effects. The most frequently reported side effects were symptoms of behavioral disinhibiton (n=5; 45.45%). The medication was discontinued in three subjects (27.27%) due to side effects, mainly symptoms of behavioral disinhibiton.

Conclusions: A cautious trial of escitalopram may be helpful in preschool children with anxiety disorders with significant impairment and/or who are non-responsive to psychosocial interventions. Preschool children may be more vulnerable to develop side effects, particularly behavioral disinhibition.

Key words: Children, preschool, anxiety disorder, pharmacotherapy, escitalopram

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INTRODUCTION

There has been significant improvement in understanding and treatment of psychiatric disorders among school aged children and adolescents during the last decades. However there is very limited literature on the characteristics of psychiatric disorders and the use of different treatment modalities, including psychopharmacological agents, among preschool children (1,2). Despite the fact that there is no clear consensus on the treatment of preschool children with psychiatric disorders, the primary treatment modality for most very young children is generally psychotherapeutic rather than psychopharmacological (2,3). Of preschoolers with psychiatric disorders, only a small proportion are referred for mental health treatment. A review by Gleason et al. (2007) stated that the risks associated with untreated psychiatric disorders are significant in preschool children and can be associated with childcare expulsion, inability to participate in family activities, impaired peer relationships, and high-risk behaviors (2). Cognitive behavioral therapy (CBT) involving parents is recommended as the first choice for the treatment of psychiatric disorders, including anxiety disorders in preschool children (2). Gleason et al. (2007) further suggested that psychopharmacological treatment of preschool anxiety disorders should be considered if the symptoms cause significant distress or severe impairment in a child's relationships, daily routine at home, or in the child-care setting (2). Regarding psychopharmacological treatment in preschool children, more prominent data come from several studies on the efficacy and safety of methylphenidate in preschool children with attention-deficit hyperactivity disorder (4-6) and risperidone in preschool children with autism spectrum disorders (7,8) or disruptive behavior disorders (9). However there are no randomized controlled studies of psychopharmacological interventions with preschoolers with anxiety, trauma-related or obsessive-compulsive disorders. The existing literature is generally limited to several case reports or series. There are only several case reports on the efficacy of fluoxetine (10) or sertraline (11) in preschool children with OCD and the efficacy of fluoxetine in a preschool girl with multiple anxiety disorders (12). The present study is a case series of eleven preschool children with anxiety disorders whose symptoms did not respond to or improve with psychosocial interventions. They were eventually treated with escitalopram.

METHODS

Participants

Subjects in this study were preschool children treated with escitalopram for anxiety related emotional/behavioral problems. They were referred and followed up in a private child psychiatry clinic (PEDAM; Center for Psychiatric Research, Training and Consultation) in the city center of Istanbul, Turkey. The majority of the parents had sought help from a psychologist or school consultant before referral but they usually could not achieve any improvement. None of the subjects had received psychopharmacological treatment before referral.

Assessment & Data Collection

Data for this study were collected by reviewing the medical records of the subjects. Subjects were referred to the clinic for a variety of emotional and behavioral problems. All subjects presented in the clinic were initially assessed for reason(s) for referral, developmental and medical history, presence and severity of psychiatric disorders/symptoms, and the need for a particular treatment. Upon diagnostic psychiatric examination using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria, all subjects received a diagnosis of one or more anxiety disorders with or without other comorbid disorders. The subjects were scheduled for a psychosocial intervention program including family education, cognitive-behavioral and play therapy after diagnostic evaluation. Psychosocial interventions were designed depending on the case characteristics, family's ability to cooperate and afford the program and presence of clinical resources. The medical records of the subjects revealed that they were started escitalopram to treat anxiety related emotional/behavioral problems after a period of 2 to 9 weeks. Psychopharmacological treatment was deemed necessary in these subjects, because they continued to experience significant distress and functional impairment despite all possible psychosocial interventions being implemented.

Before escitalopram was started, all parents were informed about their child's diagnosis, and possible outcomes and side effects of psychopharmacological treatment. The majority of the parents were familiar with psychopharmacological treatment from their own past or

current experience. Children whose parents consented for psychopharmacological treatment were started on escitalopram 1 or 2 mg/day and the dosage was increased according to the clinical response and emergence of the side effects. The Clinical-Global Impression-severity (CGI-S) and improvement (CGI-I) scales were used to rate symptom severity and improvement in target symptoms. Subjects were reassessed every 2-4 weeks after escitalopram treatment was started to rate clinical improvement and to ascertain treatment related side effects. Improvement was defined as the remission of target anxiety symptom(s) and/or functional impairment related to these anxiety symptom(s). Improvement was measured on the basis of parental reports, clinical observations and teacher's reports when available. A side effect check list was used to ascertain treatment related side effects. The side-effect checklist included symptoms of behavioral disinhibition (SBD) that Coskun and Zoroglu (2009) (10) and Liebowitz et al. (2002) (14) reported in their fluoxetine study among preschool and school-aged children and adolescents with OCD. Baseline and follow-up assessments were conducted by an experienced child psychiatrist (M.C.) who has particular interest in preschool psychopathology and pediatric psychopharmacology.

RESULTS

The subjects were eight girls and three boys with an age range of 47 to 64 months (55.45±5.90 months) at the time of starting escitalopram treatment. The DSM-IV diagnoses among the sample included obsessive compulsive disorder (OCD) (n=6), attention deficit hyperactivity disorder (ADHD) (n=4), oppositional defiant disorder (ODD) (n=3), post-traumatic stress disorder (PTSD) (n=3), separation anxiety disorder (SAD) (n=2), social phobia (SoP) (n=2), special phobia (SP) (n=2), elimination disorder (ED) (n=2), generalized anxiety disorder (GAD) (n=1), tic disorder (TD) (n=1), and gender identity disorder (GID) (n=1). None of the subjects received a diagnosis of mental retardation or autism spectrum disorders. Table 1 shows the clinical characteristics, target symptoms and improvement of the subjects.

Initial and maximum dosages of escitalopram ranged between 1-2 mg/day (1.81±0.40 mg/day) and 2-10 mg/day (3.72±2.49 mg/day; median 3 mg/day) respectively. The duration of escitalopram treatment ranged between 2 and 20 weeks (mean 8.54±5.12 weeks; median 10 weeks).

Five subjects showed mild to very much improvement and one subject who discontinued medication due to side effects showed no improvement in OCD symptoms on the CGI-I scale. Three subjects showed moderate to much improvement in anxiety symptoms that included separation, social and generalized anxiety and animal and lightning phobias. Three subjects showed mild, moderate or much improvement in PTSD symptoms. One subject showed very much improvement in pica.

Overall two subjects, cases 4 and 6 did not report any side effects. Most frequently reported side effects were symptoms of behavioral disinhibiton (SBD). Five subjects developed SBD (45.45%) which included emergence or increase in irritability (n=5), emergence or increase in hyperactivity (n=4), emergence or increase in oppositional behaviors (n=4), risky behaviors (n=3), emergence or increase in verbal and/or physical aggression (n=3), excessive talking (n=3) and self injurious behavior (n=1). SBD emerged in these subjects after 2 to 20 days of escitalopram treatment. SBD emerged after the first initial dosage in four subjects (cases 2,7,9,10) and after dosage increase in another subject (case 5).

Other side effects included decreased appetite (n=4), emergence or increase in enuresis (n=3), sleep disturbances (n=3), increased appetite (n=2), flu-like symptoms (n=2), yawning (n=2), weight loss (n=2; 1000 and 3000 grams), abdominal pain (n=2), headache (n=2), fatigue (n=1), encopresis (n=1), itching (n=1), thumb sucking (n=1), sedation (n=1), leg pain (n=1), increased water consumption (n=1), dry mouth (n=1), frequency (n=1) and constipation (n=1). Medication was discontinued in three subjects, cases 7, 9 and 10 (27.7%) after 2 or 3 weeks due to significant SBD. SBD disappeared or returned to pre-treatment level within three weeks after discontinuation in these subjects. No one of the subjects developed suicidal ideation and/or suicidal behavior at any time during treatment.

As concomitant medication two subjects (cases 3 and 9) had been receiving hydroxyzine 5-10 mg/day for some periods during escitalopram treatment for sleep problems. One subject (case 10) had been receiving risperidone 0.25-0.5 mg before and during escitalopram treatment and another subject (case 2) was started on risperidone 0.25-0.5 mg after escitalopram was initiated. Risperidone was started in these subjects for the treatment of behavioral problems related to ADHD and ODD.

Table 1: Clinical Characteristics, Target Symptoms and Improvement of the Subjects

Case	Age (months)/Sex/ DSM IV Diagnosis	Dosage / Duration of Treatment	Target Symptoms	CGI Improvement in Target Symptoms
1	54/F/ SAD, GAD	2-10 mg/d; 20 wks	Anxiety symptoms	Moderate to much improvement
2	63/F/ OCD, SP, ADHD, ODD, Pica	2-3 mg/d; 12 wks	Obsessions Pica	Much improvement Very much improvement
3	48/F/ PTSD, ED	1-2 mg/d; 10 wks	PTSD symptoms	Moderate improvement
4	64/F/ SAD, SoP	2-5 mg/d ; 10 wks	Anxiety symptoms	Moderate to much improvement
5	63/F/ OCD, TD	2-6 mg/d ; 8 wks	OCD symptoms	Mild improvement
6	56/F/ PTSD	2 mg/d ; 6 wks	PTSD symptoms	Much improvement
7	54/M/ADHD, OCD, ODD	2 mg/d ; 3 wks	OCD symptoms	Moderate improvement
8	55/M/ OCD	2-4 mg/d ; 10 wks	OCD symptoms	Very much improvement
9	47/F/ ADHD, PTSD, ED	2-1 mg/d ; 3 wks	PTSD symptoms	Mild improvement
10	56/M/ ADHD,ODD,OCD	2 mg/d ; 2 wks	OCD symptoms	No improvement
11	50/F/ OCD, SP, SoP, GID	1-3 mg/d ; 10 wks	OCD symptoms Anxiety symptoms	Moderate improvement Moderate improvement

ADHD: Attention deficit hyperactivity disorder; ED: Elimination disorder; F: Female; GAD: Generalized anxiety disorder; GID: Gender Identity disorder; M: Male; OCD: Obsessive compulsive disorder; ODD: Oppositional defiant disorder; PTSD: Post-traumatic stress disorder; SAD: Separation anxiety disorder; SoP: Social Phobia; SP: Special phobia; TD: Tic disorder

DISCUSSION

There have been several lines of evidence that selective-serotonin reuptake inhibitors (SSRIs) are generally safe and effective, in varying degrees, in treating anxiety (15-18), trauma-related (19-21) and obsessive-compulsive disorders (14, 22) in school aged children and adolescents. Despite the fact that escitalopram has been approved for those above 12-years of age, it has been reported to be effective and well tolerated in children and adolescents with anxiety (23), and in adolescents with major depressive disorders (24). However data related to psychopharmacological treatment of anxiety disorders in preschoolers are scant. To our knowledge this is the first report on the psychopharmacological treatment of preschool anxiety disorders with escitalopram. The rationale behind escitalopram preference could be the fact that it comes in liquid form that may facilitate oral administration and dosage titration in these very young subjects.

Escitalopram was generally effective in abating anxiety, post-traumatic and obsessive-compulsive symptoms in these subjects. It was started at 1 or 2 mg/day dosages and increased up to 10 mg/day according to the clinical response and tolerability. However the majority of the subjects showed significant improvement at lower dosages and the mean maximum dosage was 3.72 mg/day. Five subjects with distressing symptoms of OCD showed mild to very much improvement while one subject with a diagnosis of OCD who discontinued medication due to side effects after two weeks showed no improvement. Three subjects showed moderate to much improvement in several anxiety disorders such as separation, generalized, social anxiety disorders and severe animal and lightning phobias. Three subjects showed mild to much improvement in PTSD symptoms, and one of them discontinued medication due to side effects after three weeks.

One of the important findings could be the relatively high rates of side effects related to escitalopram treatment in these very young subjects. While two subjects reported no side effects (18.18%), the majority of the subjects (n=9; 81.81%) reported at least one side effect. This ratio of side effects is higher than previous reports of SSRI related side effects in children and adolescents (25,26). However only three subjects discontinued the medication due to side effects (27.27%) and side effects were transient and/or mild to moderate in severity which did not require medication discontinuation in the majority of them. Medication was discontinued in three subjects after 2 or 3 weeks due to significant SBD. Those subjects exhibited

aggressive, oppositional, risky and self injurious behaviors (such as jumping from height or into the roads, dangerous play activities, head banging) in addition to hyperactivity and irritability. Behavioral disinhibition is a more common condition than a (hypo)manic reaction during SSRIs treatment and it is differentiated from a (hypo)manic reaction by the absence of more specific manic symptoms such as elevated mood and grandiosity (25-27). It has been previously suggested that the presence of ADHD may be associated with increased risk of developing SBD during SSRI treatment in children, and young children may be at higher risk of developing these behavioral side effects than adolescents or adults (27). This may be consistent with our findings that four of the five subjects who developed SBD had comorbid ADHD with or without ODD.

Safer and Zito (2006) investigated treatment-emergent adverse events from SSRIs in children and adolescents (26). They found that side effects related to behavioral activation were 2- to 3-fold more prevalent in children than in adolescents. Meanwhile Gualtieri and Johnson (2006) reported that 28% of children and adolescents on various "modern" antidepressants, including SSRIs, experienced behavioral adverse effects (25). Zuckerman et al. (2007) reviewed the tolerability of SSRIs in 39 children under the age of 7 years and found that 28% had an adverse event of at least moderate severity, with behavioral activation being the most prevalent side effect (21%) (13). Seven subjects (18%) discontinued the SSRIs due mainly to behavioral side effects. Because this study did not include escitalopram among the study medications, the current study is the first report on the use of escitalopram in preschool children. In a recent study of fluoxetine in preschool children with OCD, Coskun and Zoroglu (2009) reported SBD in five of the six subjects (83%) and the medication was discontinued in one subject (16.6%) due to SBD (10). For the current study, the rates of SBD and discontinuation due to SBD were 45.45 and 27.27 percents respectively. When we consider the findings from these studies, it could be suggested that SBDs are the most frequently reported side effects and most frequent reason for medication discontinuation in preschool children treated with SSRIs.

This study was a case series providing data about the efficacy and tolerability of escitalopram in preschool children with anxiety disorders. It has several inherent methodological limitations, such as the retrospective and uncontrolled design, small sample size and lack of validated instruments in the severity and improvement assessment that make it difficult to generalize from the findings of this study. Research on the clinical characteristics and treatment of psychiatric disorders in preschool children is still in an early stage. Escitalopram was effective in abating anxiety, trauma-related and obsessive-compulsive symptoms in these subjects, although the majority of the subjects reported at least one side effects and a relatively high ratio of discontinuation due to side effects. However side effects were generally mild to moderate in severity, no life-threatening side effects were reported and side effects that led to medication discontinuation were reversible. Preschool children seem to be more vulnerable to the behavioral side effects of the SSRIs and discontinuation rates due to side effects may be higher in this age group than school aged children and adolescents. There is a need for further studies on the treatment of preschool psychopathology while balancing ethical considerations, short and long term unwanted effects of treatment and the therapeutic needs of preschool children.

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