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# Fluoxetine for the Treatment of Childhood and Adolescence Social Phobia: Factors playing a role in Efficacy

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**ÖZET:**

Çocuk ve ergenlerde sosyal fobi tedavisinde fluoksetin: Etkinlikte rol alan faktörler

**Amaç:** Bu çalışmanın amacı 7-17 yaş aralığındaki sosyal anksiyete bozukluğu (SAB) bulunan çocuk ve ergenlerde (n: 40) fluoksetinin 8. ve 12. haftalardaki etkinliğini araştırmak ve tedaviye yanıtı etkileyen faktörleri tespit etmektir.

**Yöntem:** Çalışma natüralistik bir desende yapıldı ve sonuçlar geriye dönük olarak değerlendirildi. İlk başvuruda çocuklara Klinik Global İzlem Ölçeği, Çocuklar İçin Sosyal Anksiyete Ölçeği, Çocuklar için Sosyal Fobi Ölçeği-Yenilenmiş (ÇİSFÖ-Y) ve annelere Liebowitz Sosyal Fobi Belirtileri Ölçeği uygulandı. 8 ve 12. haftalarda hastalar Klinik Global İzlem Ölçeği ile değerlendirildi ve olgular ÇİSFÖ-Y'yi doldurdular.

**Bulgular:** Fluoksetin SAB'de anlamlı olarak etkili bulunmuş ve hastalar tarafından iyi bir şekilde tolere edilmiştir. Olumlu etkisinin zaman içerisinde arttığı görülmüştür. En iyi lineer kombinasyonu belirlemek amacıyla eşlik eden anksiyete bozukluğu varlığı, temel ÇİSFÖ-Y puanları, SAB'nin süresi, maternal sosyal anksiyete skoru, depresyon ve anksiyete bozuklukları için aile öyküsü için bir çoklu regresyon modeli oluşturulmuştur. 12. haftadaki ÇİSFÖ-Y puanlarında bu değişkenler kombinasyonu için anlamlı bir farklılık saptandı F(6,99)=91.5, p:0.01.

**Sonuç:** Bu çalışmanın bulguları çocuk ve ergenlerdeki sosyal anksiyete bozukluğunda fluoksetin kullanımının etkin ve güvenilir olduğunu göstermiştir. Sonuçlara göre, küçük yaşın, düşük bazal sosyal anksiyete skorunun, ailede depresyon veya anksiyete bozukluğu öyküsü olmamasının, annenin sosyal anksiyete skorunun düşük olmasının daha iyi tedavi yanıtıyla ilişkili olduğu bulunmuştur. Öte yandan, örtüşen anksiyete belirtileri var olmaya devam etse de, komorbid anksiyete bozukluğu olan çocuk ve ergenlerde sosyal anksiyete bozukluğunun iyileşme olasılığı daha yüksek bulunmuştur.

**Anahtar sözcükler:** Sosyal anksiyete, sosyal fobi, fluoksetin, çocuk, ergen

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**ABSTRACT:**

Fluoxetine for the treatment of childhood and adolescence social phobia: factors playing a role in efficacy

**Objective:** The aim of this study was to investigate the stepwise efficacy, after 8 and 12 weeks of fluoxetine treatment, on social anxiety disorder (SAD) in 7 to 17 year-old children and adolescents (n=40) and to explore the variables that determine the response to treatment.

**Method:** The study had a naturalistic design where the results were analyzed retrospectively. The baseline measures included the Clinical Global Impression-Severity, the Self-Report for Childhood Anxiety Related Disorders, the Social Anxiety Scale for Children-Revised (SASC-R), and the maternal Liebowitz Social Anxiety Scale. At 8 and 12 weeks, patients were rated on the Clinical Global Impression-Improvement, while children and adolescents completed the Self-Report for Childhood Anxiety Related Disorders.

**Results:** Fluoxetine was significantly effective for SAD and well tolerated. The beneficial effect increased over time. A multiple regression model was constructed to determine the best linear combination of age, presence of a comorbid anxiety disorder, baseline SASC-R scores, duration of SAD, maternal social anxiety scores, and family history for depression and anxiety disorders. This combination of variables significantly predicted the SASC-R scores at 12 weeks (F(6,99)=91.5, p=0.01).

**Conclusion:** The results of this study reveal that fluoxetine is effective and well tolerated for the acute treatment of social anxiety disorder in children and adolescents. The results suggest that younger age, lower baseline social anxiety scores, absence of a family history for depression and/or anxiety disorders, and lower maternal social anxiety scores predict a better outcome. Although overlapping anxiety symptoms of comorbid disorders may persist, the improvement of SAD is more likely when the children or adolescents have a comorbid anxiety disorder.

**Key words:** Social anxiety, social phobia, fluoxetine, child, adolescent

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## INTRODUCTION

Social anxiety disorder (SAD), also known as social phobia, is defined by the presence of excessive fear of social or performance situations in which a person is exposed to scrutiny or possible humiliation (1). Approximately 5% of youths suffer from social phobia (1), the third most common psychiatric disorder in the United

States (2). Large epidemiological studies have found rates of DSM-IV SAD to be 0.5% in children and 2.0% to 4.0% in adolescents (3,4). The mean age of onset for SAD is often reported as occurring during adolescence (5); however, studies also support earlier onset, between the ages of 7 and 8 years old (6). Early onset predicts a more severe and chronic course (7,8) and is associated with occupational and social impairment in adulthood (9). In a cohort study, the authors concluded that it would be particularly useful in classifying the large number of subjects who receive treatment but don't meet the full DSM-III-R criteria for social phobia, because those with subthreshold and symptom-level diagnoses accounted for 61% of those who had sought treatment for symptoms of social phobia (9). Despite its prevalence, most of adolescents do not receive treatment (10).

Childhood-onset anxiety disorders predict adult anxiety and depressive disorders and cause significant psychosocial and work impairment during adulthood (11,12), indicating the need for early and effective treatments. Similar to other anxiety disorders, SAD is often associated with family, school, and social problems, increased risk for depression, and substance abuse (13). Children and adolescents with SAD have lower social skills, less frequently participate in social activities, and often feel lonely (14). They may have a lower self-esteem and less motivation in daily activities, which may also lead to poor academic performance (15). If not successfully treated, SAD may persist into adulthood (12,13,16).

Although childhood anxiety disorders are common and are accompanied by significant morbidity, data supporting the efficacy of pharmacological treatments for youths with anxiety disorders other than obsessive-compulsive disorder are scarce (17). Compared to cognitive-behavioral therapy (CBT), pharmacotherapy has not been as thoroughly studied for childhood anxiety disorders (18,19). Several recent studies suggest that selective serotonin reuptake inhibitors (SSRIs) have therapeutic effects for anxiety disorders in children and adolescents and they are suggested as first-line treatment because of their relatively safe side-effect profiles (17,18,20). In adults, social phobia response rates for SSRIs range from 36% to 77%, although remission rates are typically lower and some youths are still symptomatic post-treatment (10).

Research has begun to examine predictors of treatment response among youth with heterogeneous anxiety disorders. However, emerging data reveal these disorders to represent distinct constructs with unique features and impairments and potentially unique etiological mechanisms (21). Compared to those in adults, examinations of mediators and moderators of treatment outcome in anxious children are rare (21).

The aim of this study was to investigate the stepwise efficacy, at 8 and 12 weeks of fluoxetine treatment, in childhood and adolescence SAD, and to explore the predictive value of several variables (e.g., age, gender, presence of a comorbid anxiety disorder, parental social anxiety, etc.) that may be associated with better outcomes.

# METHODS

## Setting and Subjects

The study had a naturalistic design where the results were analyzed retrospectively. In a clinical sample, during a 12 month period fluoxetine treatment-naive 7 to 17 year-old children and adolescents, who fulfilled the DSM-IV criteria for social anxiety disorder (SAD) (generalized type) and who were prescribed fluoxetine, were included (n=70). Among the sample defined above, subjects with current major depressive disorder (n=5), adjustment disorder (depressive subtype) (n=2); a history of psychotic episodes (n=1), active epilepsy (n=1) and subjects on concurrent psychopharmacological medication (n=15) or with a history of previous medication for social anxiety disorder (n=10) were excluded. Thus, the study sample included forty cases (male, n=23; female, n=17), who were 7 to 17 (mean: 11.08±2.9) years old. This study was carried out in accordance with the Helsinki Declaration of the World Medical Association. The Institutional Review Board approved the protocol of this study. Informed parental consent was obtained for all children before their inclusion in the study.

## Measures

### A. Psychiatric Diagnosis

The Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T) (22,23) is a structured diagnostic assessment schedule based on the DSM-IV criteria for major psychiatric disorders. It is an effective instrument

for diagnosing major childhood psychiatric disorders. The validity of K-SADS-PL-T was found to be excellent for elimination disorders, good for attention deficit and hyperactivity disorder and tic disorders and fair for affective disorders, anxiety disorders and oppositional defiant disorder. The interrater reliability was observed to be excellent for elimination disorders and tic disorders and good for attention deficit and hyperactivity disorder and anxiety disorders.

**B. The Scales Used in Rating Children**

B.1. The Social Anxiety Scale for Children-Revised (SASC-R) is an 18-item self-report instrument. Items are rated on a five-point scale ranging from 1 ("never") to 5 ("almost always"). SASC-R was developed and revised by La Greca and Stone (24). The reliability and validity study of the SASC-R-Turkish was conducted by Demir et al. (25) with 9-16 year-old children and adolescents (n=452). They reported high internal consistency (Cronbach $\alpha$=0.81), test retest reliability (r=0.81), and they concluded that the SASC-R is a reliable and valid tool to measure social anxiety in children and adolescents.

B.2. The Social Phobia Scale for Children and Adolescents (SPS-CA) is a 25 item self-report instrument and similar to the SASC-R; items are rated on a five-point scale ranging from 1 ("never") to 5 ("almost always"). The SPS-CA was developed by Demir et al (26) for the recognition, rating and follow-up of social phobia in children and adolescents. In the reliability and validity study (26), it is suggested that it is a reliable and valid additional tool (together with the SASC-R) for evaluation of social phobia symptoms in children and adolescents. While, the SASC-R assesses state social anxiety, the SPS-CA assesses trait anxiety.

**C. Scales Used in Rating Parents**

C.1. The Liebowitz Social Anxiety Scale (LSAS) is composed of two scales, one measures social anxiety and the other measures avoidance and/or social withdrawal (27). Each scale contains 24 items and items are rated on 1-4 type Likert scale. The reliability and validity study of the LSAS-Turkish was conduced by Soykan et al (28) with adult patients. They reported that the LSAS significantly differentiated adults with SAD from the healthy control group and other anxiety disordered groups.

**D. Clinician-Rated Anxiety Instruments**

D.1. The Clinical Global Impressions (CGI) scales (29) were used to measure global improvement and severity. CGI-Severity (CGI-S) provides a rating of baseline severity ranging from 1 (not at all ill) to 7 (extremely ill). CGI-Improvement (CGI-I) provides a rating of clinical improvement ranging from 1 (very much improved) to 7 (very much worsened).

D.2. Overall functioning was evaluated with the Clinical Global Assessment Scale (CGAS) (30).

## Procedures

The study had a naturalistic design where the baseline parameters were collected for another study on clinical aspects of SAD. Therefore, the results were analyzed retrospectively. At intake, all patients were assessed clinically and the psychiatric clinical diagnosis was based on a comprehensive evaluation of the patients. Additionally, child and adolescent psychiatry residents, under the supervision of a specialist, interviewed children and parents using the K-SADS-PL-T (22). The baseline measures included CGI-S, CGAS, SASC-R, SPS-CA, and LSAS. The retrospective analysis covered three phases: first phase: baseline, second phase: 7-10 [mode=8] weeks, and third phase: 11-14 [mode=12] weeks after the initial medication. In the second and third phases, child and adolescent psychiatry specialists rated the CGI-I and CGAS, while children and adolescents completed the SASC-R and SPS-CA. No other form of treatment (e.g., cognitive-behavioral therapy) was applied in addition to the fluoxetine during the trial.

# STATISTICS

Variable distributions were examined for normality and nonparametric statistics were used in the cases of abnormal distributions. The repeated-measures ANOVA or Friedman tests were used to assess the significance of differences in the CGI, CGAS, SASC-R and SPS-CA scores between baseline and the second and third phases. For each measurement, where the Friedman test revealed a significant difference, a Wilcoxon test was computed to explore the source of the significance. Given that three post hoc comparisons were made, it would be desirable to

make a Bonferroni correction on alpha, such that p would need to be .05/3 ( about .017) to be significant. For all comparisons, treatment effects were evaluated by using "intent-to-treat" analyses with the last observation carried forward. In the exploratory post hoc analyses, the group was divided into two, in terms of improvement in the SAD symptoms after fluoxetine treatment, as "improved" (IMP) and "not-improved" (N-IMP). The patients whose CGI-I decreased to ≤2 in the 12-week trial were assumed to be IMP and the others to be N-IMP. Student t tests and chi-square tests were used to measure differences between the two groups, in terms of sex, age, symptom severity, comorbidity, and baseline measurement scores. The predictors of response were assessed with multiple regression models and predictors included age, sex, severity of anxiety symptoms at intake, duration of illness, presence of comorbid anxiety disorders, CGI-S score, CGAS scores, maternal and paternal social anxiety scores, and family history of anxiety or mood disorders. All p values are based on two-tailed tests with $\alpha = .05$. All values are reported as either percentages or means ± standard deviation. SPSS 11.0 was used for all statistical calculations.

## RESULTS

The mean baseline Clinical Global Impressions-Severity (CGI-S) rating was 4.47±0.9 (3-6). Most subjects had baseline Clinical Global Impressions-Severity (CGI-S) ratings of moderately ill (CGI-S=4, n=17, 42.5%) or markedly ill (CGI-S score of 5, n=12, 30%). Six subjects were rated severely ill (CGI-S score of 6, 15%), five subjects were rated mildly ill (CGI-S score of 3, 12.5%), and no subject was rated among the most extremely ill patients (CGI-S score of 7, 0%). Eight patients (20%) had one comorbid anxiety disorder (generalized anxiety disorder (GAD) [n=6]; specific phobia [n=1]; obsessive-compulsive disorder [n=1]), and one had selective mutism [n=1]. One patient had two comorbid anxiety disorders (GAD and separation anxiety disorder). Other comorbid disorders were stuttering (n=5, 12.5%), attention deficit hyperactivity disorder (n=3, 7.5%), enuresis nocturna (n=2, 5%), and chronic motor tic disorder (n=1, 2.5%).

Seven (17.5%) patients reported adverse effects of fluoxetine including gastrointestinal symptoms (n=3), headache (n=2). Two patients discontinued medication because of side effects (both had an increase in irritability). Thirty-eight (95%) out of forty subjects completed the 8$^{th}$ week, and thirty-one (77.5%) completed the 12$^{th}$ week assessment. The baseline, second, and third phase scores of the children and adolescents are presented in Table 1. The baseline, second, and third phase SPS-CA, SASC-R, CGAS, and CGI for SAD scores of the children and adolescents were found to be significantly improved at each time point.

In the exploratory post hoc analyses, the group was divided into two, in terms of improvement in the SAD symptoms after fluoxetine treatment; the patients whose CGI-I decreased to ≤2 in the third phase were assumed as "improved" (IMP) (n=24) and the others as "not-improved" (N-IMP) (n=16). The baseline scores of IMP and N-IMP are presented in Table 2. Age group, maternal LSAS-anxiety scores, and presence of any comorbid anxiety disorder were significantly different between IMP and N-IMP groups.

A multiple regression model was conducted to determine the best linear combination of age, presence of a comorbid anxiety disorder, baseline SASC-R scores, duration of SAD, maternal social anxiety scores, and

**Table 1: The baseline, second, and third phase scores of the children and adolescents**

| | Baseline (1) mean±SD | 2$^{nd}$ Phase (7-10$^{th}$ week) (2) mean±SD | 3$^{rd}$ Phase (11-14$^{th}$ week) (3) mean±SD | $\chi^2$ | df | p | Source of significance** |
|---|---|---|---|---|---|---|---|
| CGI for SAD | 4.47±0.9 | 3.05±0.8 | 2.48±0.7 | 64 | 2 | <0.001* | 1:2, 1:3, 2:3 |
| CGAS | 63.38±8.0 | 74.75±8.6 | 80.50±7.8 | 59 | 2 | <0.001* | 1:2, 1:3, 2:3 |
| SASC-R | 49.95±12.2 | 40.23±12.3 | 37.78±10.6 | 52 | 2 | <0.001* | 1:2, 1:3, 2:3 |
| SPS-CA | 61.03±15.6 | 51.63±15.2 | 48.47±12.7 | 41 | 2 | <0.001* | 1:2, 1:3, 2:3 |

*Friedman Tests, **Wilcoxon Tests, CGI: Clinical Global Impression, CGAS: Clinical Global Assessment Scale, SAD: Social anxiety Disorder, SASC-R: Social Anxiety Scale for Children-Revised, SPS-CA: Social Phobia Scale for Children and Adolescents

**Table 2: The baseline scores of Improved (IMP) and not-Improved (N-IMP)**

| | IMP (n: 24) mean±SD | N-IMP (n:16) mean±SD | t | df | p |
|---|---|---|---|---|---|
| Child/ Adolescent | | | | | |
| Age (years) | 10.29±2.6 | 12.25±3.0 | -2.1 | 30 | 0.03 |
| CGI for SAD | 4.38±0.9 | 4.63±0.9 | -0.8 | 30 | 0.4 |
| CGAS | 61.67±5.2 | 65.94±10.7 | -1.6 | 38 | 0.1 |
| SASC-R | 50.92±10.6 | 48.50±14.7 | 0.6 | 25 | 0.6 |
| SPS-CA | 61.00±12.7 | 61.06±19.6 | -0.1 | 38 | 1.0 |
| Parent | | | | | |
| Maternal LSAS-Anxiety | 42.77±11.6 | 54.00±1.4 | -3.3 | 13 | 0.006 |
| Paternal LSAS-Anxiety | 41.80±13.1 | 47.00±8.5 | -0.7 | 2 | 0.5 |
| | **n (%)** | **n (%)** | $\chi^2$ | **df** | **p** |
| Gender | | | | | |
| Male | 13 (56.5) | 10 (43.5) | 0.3 | 1 | 0.7 |
| Female | 11 (64.7) | 6 (35.3) | | | |
| Comorbid anxiety disorder | | | | | |
| Present | 9 (90.0) | 1 (10.0) | 5.0 | 1 | 0.027* |
| Absent | 15 (50.0) | 15 (50.0) | | | |
| Age groups (years) | | | | | |
| 7-12 | 20 (71.4) | 8 (28.6) | 5.0 | 1 | 0.029* |
| 13-17 | 4 (33.3) | 8 (66.7) | | | |
| Positive family history for depression and/oranxiety† | | | | | |
| Present | 7 (50.0) | 7 (50.0) | 7.6 | 1 | 0.3 |
| Absent | 8 (66.6) | 4 (33.3) | | | |

*Fisher's exact test because of small cells.
CGI: Clinical Global Impression, CGAS: Clinical Global Assessment Scale, LSAS: Liebowitz Social Anxiety Scale, SAD: Social anxiety Disorder, SASC-R: Social Anxiety Scale for Children-Revised, SPS-CA: Social Phobia Scale for Children and Adolescents

**Table 3: Means, Standard Deviations, and Intercorrelations for 12th week SASC-R scores and Predictor Variables**

| Variable | M | SD | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|
| SASC-R Score (12th week) | 36.77 | 12.3 | -.08 | .85** | -.15 | .50 | .58* | .24 |
| Predictor variable | | | | | | | | |
| 1. Age (years) | 10.44 | 1.9 | - | -.42 | -.25 | -.44 | -.18 | .06 |
| 2. Baseline SASC-R Score | 51.44 | 13.2 | | - | .22 | .64* | .50 | -.06 |
| 3. Duration of SAD (months) | 46.56 | 20.4 | | | - | .33 | -.25 | -.68* |
| 4. Presence of comorbid anxiety disorder | 1.33 | .5 | | | | - | .50 | -.52 |
| 5. Presence of a family history of depression and/or anxiety disorder | 1.33 | .5 | | | | | - | -.18 |
| 6. Maternal LSAS Score | 98.56 | 10.4 | | | | | | - |

*p<.05; **p<.01

family history for depression and anxiety disorders. The means, standard deviations, and intercorrelations can be found in Table 3. This combination of variables significantly predicted third phase SASC-R scores ($F(6,99)=91.5$, $p=0.01$). The beta weights, presented in Table 4, suggest that older age, higher baseline SASC-R scores, presence of a comorbid anxiety disorder, presence of a family history of depression and/or anxiety disorder, and higher maternal social anxiety scores contribute most to predicting higher SASC-R scores at 11-14 weeks' of treatment. The adjusted R squared value was .98. This indicates that 98% of the variance in SASC-R scores at 11-14 weeks of treatment was explained by the model. According to Cohen (31), this is a large effect.

**Table 4: Simultaneous Multiple Regression Analysis summary for age, baseline SASC-R scores, presence of a comorbid anxiety disorder, presence of a family history of depression and/or anxiety disorder, and maternal social anxiety scores predicting 12th weeks' SASC-R Scores**

| Variable | B | SEB | β |
|---|---|---|---|
| 1. Age (years) | 2.90 | .35 | .44* |
| 2. Baseline SASC-R Score | .50 | .08 | .53* |
| 3. Duration of SAD (months) | .17 | .06 | .28 |
| 4. Presence of comorbid anxiety disorder | 11.51 | 1.99 | .47* |
| 5. Presence of a family history of depression and/or anxiety disorder | 8.94 | 1.99 | .36* |
| 6. Maternal LSAS Score | .87 | .13 | .74* |
| Constant | -139.7 | 17.4 | |

Note. $R^2$=.98; F(6,99)=91.5, p:0.01, *p<.05; **p<.01

## DISCUSSION

The results of this study reveal that fluoxetine treatment is beneficial in childhood and adolescent SAD, and that it is well tolerated except for mild and transient headaches and gastrointestinal side effects. Only two (5%) of the patients discontinued the medication because of side-effects (increase in irritability). Thus, the results are in favor of fluoxetine treatment for childhood SAD.

Previously, open studies using fluoxetine for anxious children and adolescents who failed to respond to other treatments, suggested that it was beneficial and well tolerated for the treatment of anxiety in youths (32-38). Therapeutic efficacy of fluoxetine in anxiety disorders may be delayed as long as 12-weeks, and if necessary, dose adjustment is suggested for every 2 to 3 weeks (20).

Small, randomized, placebo-controlled trials (RCTs) have demonstrated efficacy and tolerability of SSRIs for SAD (n=15) (39). Similarly in a previous open-label study, where fluoxetine was administered at a dose of 25.7 (10-60) mg/day on average for 6-8 weeks to 11-17 year-old children and adolescents with SAD (n=21), 81% of them showed significant improvements in SAD symptoms (33). In another study, fluoxetine was given to children and adolescents with SAD who previously did not respond to psychotherapy at doses of 24 mg/day (children) or 40 mg/day (adolescents) on average for 6-9 weeks, and 80% of the patients showed improvement (38). In a 12-week RCT, Birmaher et al. (17) showed that fluoxetine (n=37) was significantly more effective than placebo (n=37) for the treatment of children and adolescents with SAD, generalized anxiety disorder, and/or separation anxiety disorder. Five patients discontinued fluoxetine treatment because of side effects (increase in the hyperactivity and disinhibition). Birmaher et al. (17) noted that despite improvement, many participating patients remained symptomatic. In our study, at the 11-14th week, 60% of the patients had CGI-I ≤2, which was assumed to be improvement. On the other hand, 5% discontinued medication due to side effects (irritability).

Our results suggest that a 7-10 week treatment with fluoxetine is significantly effective, and the efficacy increases over time, as the social anxiety scores were found to be significantly lower by the 11-14th week when compared to the 7-10th week scores. This finding is in accordance with a 6-month open treatment follow-up study where patients treated with fluvoxamine or fluoxetine showed additional improvement in the follow-up period (40). Similarly in another study, children and adolescents (n=42) treated with fluoxetine for their anxiety disorders were followed for one-year and the patients who continued medication had significantly lower anxiety scores than the patients who were not medicated (n=10) (18).

As described in the literature, a moderator variable affects the direction and/or strength of a relation between independent and dependent variables, whereas a mediator variable refers to any patient characteristic that is changed during treatment and can account for observed changes in dependent measures (41).

Multiple regression analysis of our results revealed that several variables significantly predicted better outcomes. First, younger age predicts a more favorable result by the 11-14th week of fluoxetine treatment. While 71.4% of the children improved, only one-third of the adolescents had a CGI-I ≤2. Previous epidemiological findings suggest that adolescents have higher rates of SAD than younger age groups. Essau and colleagues (3) have found an increase greater than twofold between a 12 to 13 year-old and a 14 to 15 year-old group (0.5% versus 2.0%, respectively), whereas Wittchen and colleagues (4) have found a twofold increase among 14 to 17 year-old and 18 to 24 year-old groups (4.0% versus 8.7%, respectively). The increasing prevalence of SAD across age groups may be understood partially as increased self-consciousness in the context of both developmental and environmental transitions (i.e., puberty, dating, new schools, peer influences, and other factors) (42). Therefore, in accordance with this assumption, in older ages, as the probability of the appearance of the

disorder increases, the efficacy of fluoxetine may diminish.

Second, higher social anxiety scores, and third, a positive family history of depression and/or anxiety disorders predicted higher scores at the end of the trial. Similarly, in another study, severity of the anxiety at intake and positive family history for anxiety predicted poorer functioning at the end of the study (17).

Fourth, in concordance with the presence of family history for anxiety disorders, higher maternal social anxiety scores predicted a less beneficial outcome. This finding supports the importance of genetic influences on the development and the course of SAD. Higher maternal social anxiety scores may indicate a stronger biological susceptibility for anxiety disorders, and as the biological vulnerability increase, therapeutic efficacy may decrease.

Finally, the presence of a comorbid anxiety disorder predicted higher scores of social anxiety during the 11-14$^{th}$ week assessment. Interestingly, the rate of improvement of SAD was significantly higher in the patients with a comorbid anxiety disorder. Fluoxetine was found to be beneficial also for other anxiety disorders , such as generalized anxiety disorder and specific phobia. Improvements in the comorbid condition, which may have an negative burden on SAD, may have an additive effect on the disappearance of social anxiety symptoms. However, in the presence of a comorbid anxiety disorder, as the anxiety symptoms overlap, higher scores on anxiety scales, including SASC-R should be expected.

The study has several limitations. First of all, this study had a naturalistic design and it was an open trial, where the results were collected retrospectively. Placebo-controlled trials are assumed to be the gold standard in the assessment of treatment efficacy. As another limitation, the effect of fluoxetine on the symptoms of comorbid anxiety disorders was not reassessed in the third phase (11-14$^{th}$ week of the trial). Therefore, the efficacy of fluoxetine on the comorbid anxiety disorders could not be explored. Age and comorbid disorders are important confounding factors in clinical studies. Therefore we conducted regression analyses. In addition, as another limitation of the study, although a multiple regression model, which revealed several variables, significantly predicted lower social anxiety scores after 11-14 weeks of treatment, the sample size was limited to computer logistic regression models to examine the predictive power of variables in the improvement of SAD.

## CONCLUSIONS

Fluoxetine is useful and well tolerated for the acute treatment of social anxiety disorder in children and adolescents. The beneficial effects of fluoxetine increase over time. The results suggest that younger age, lower baseline social anxiety scores, absence of a family history for depression and/or anxiety disorders, and lower maternal social anxiety scores predict a better outcome. Although overlapping anxiety symptoms of comorbid disorders may persist, the improvement of SAD is more likely when children or adolescents have a comorbid anxiety disorder. Investigations regarding the optimization of treatment to obtain full anxiety remission and the length of treatment necessary to prevent recurrences are warranted.

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