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Original Paper

Prescription Patterns of Antidepressants: The Effect of the Black Box Warning among Pediatric Patients

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Abstract

Introduction*: Our aim was to investigate the prescription patterns of antidepressant in the southern Israel during the years 2000 to 2005, before and after the FDA black box warning issued regarding the prescription of antidepressants in children.*

Patients and methods*: A cross sectional study. Data regarding prescription of anti-depressant drugs was examined retrospectively. All information was obtained from the computerized databases of the Clalit Health care services, southern county. Data was analyzed by using descriptive statistics, and analytical statistics. Multi-variate analysis was performed when applicable.*

Results*: When comparing the prescription rate of fluoxetine and fluvoxamine versus other SSRI's included in the health agencies warnings during the years mentioned, there was a gradual increase in the percentage of the other SSRI's until 2003 from 12.2% in 2000 to 64.2% in 2003 and then a reversal of this trend from 51.9% in 2004 to 47.8% in 2005.*

Discussion and conclusions*: This study shows that the CSM advice has not had a significant effect in reversing the rising prevalence of antidepressant prescribed to children and adolescents in primary care. It has however changed the choice of antidepressant medication chosen within the group of SSRI's.*

Keywords

SSRI, black box warning, prescription patterns

1. Introduction

Until recently, selective serotonin reuptake inhibitors (SSRIs) were among the most commonly prescribed medications in the world for the treatment of Major Depressive Disorder (MDD**),** in large part because they have been marketed as safe and effective. However, since the early 1990s, reports describe a possible association with suicidality (Leon et al., 1999). Recently, public health advisories expressing concern regarding the use of antidepressants for children were issued by the UK Committee on Safety of Medicines and the Food and Drug Administration (FDA) (Fergusson et al., 2005).

Major depressive disorder (MDD) is a common disorder, with a lifetime prevalence of about 15 percent. The disorder is recognized in adults, adolescents and children and carries with it significant morbidity and even a risk of mortality. In adults the disorder is twice to three times more prevalent in women, reaching perhaps 25%. The mean age on onset is 40 years.

Although the diagnostic category of depressive disorder in pediatric age used to be controversial, it is now well established that depressive disorders can and do occur in children and adolescents (Lewinsohn et al., 1993). The prevalence of depressive disorders is 1-2 percent of pre-pubertal children and 3-8 percent of adolescents, with a lifetime prevalence of approximately 20% by the end of adolescence. The female predominance seen in adults first emerges in adolescence (Zalsman, et al., 2006). Treatment of depression among adolescents is important, because adolescence is a crucial period of life that strongly influences a person's options for critical life choices.

Depression is an important contributor to suicidal behavior and completed suicide in adolescents (Brent et al., 1999). Furthermore, depression in youths is a risk factor for depressive disorder, suicidal risk, and long-term psychosocial impairment in adulthood (Weissman et al., 1999). Suicide is the third leading cause of death in adolescents (Arias et al., 2003). Suicide is less common in childhood and early adolescence. Suicide incidence increases markedly in the late teens and continues to rise until the early twenties, reaching a level that is maintained throughout adulthood. The most likely reason underlying the age of onset of suicide is that depression and exposure to drugs and alcohol, two significant risk factors for suicide are rare in very young children and becomes prevalent only later adolescence (Gould et al., 2003). Although suicidal ideation and attempts are more common among females, completed suicide is more common among males. This pattern of sex differences does not exist in all countries. Completed suicide is more common in 15- to 24-year old males than females in North America, Western Europe, Australia, and New Zealand. Gender rates are equal in some countries in Asia (e.g., Singapore), and in China, the majority of suicides are committed by females (Gould et al., 2003).

Mood disorder, disruptive behavior disorder (DBD), and substance use disorder (SUD) are the three types of disorders that are most prevalent within the adolescent suicide victim population (Esposito &

Clum, 2002). Among these, depressive disorders are consistently the most prevalent disorders (Gould et al., 2003). The two most prominent risk factors for completed suicide and suicidal behavior in adolescents are past suicide attempts and a diagnosis of a depressive disorder, each of which independently contributes at least a 10-30 fold increased risk for completed suicide (Apter & King, 2006).Clinically accepted treatments for major depressive disorder include various forms of psychotherapy and antidepressant medications. For first-line acute treatment of MDD in children and adolescents, the AACAP recommended psychotherapy, treatment with a selective serotonin reuptake inhibitor (SSRI), or both combined, depending on the patient, the patient's circumstances, and the severity of disease. Studies in depressed youths have shown that cognitive-behavioral therapy (CBT) and interpersonal psychotherapy are efficacious for the acute treatment of depression (Birmaher et al., 2000). Cognitive-behavioral therapy (CBT) as a treatment for MDD in youth has obtained strong empirical support for close to two decades .In the recent TADS study, it was found that compared with placebo, the combination of fluoxetine with CBT was statistically significant. Compared with fluoxetine, treatment of fluoxetine with CBT was superior. Fluoxetine alone was a superior treatment to CBT alone. The response rate for CBT alone was 43%, the response rate for medication was 61% and the response rate for combined treatment was 71%. (March et al., 2004) . But there have been few adequately powered controlled clinical trials in the area of MDD. Controlled studies of tricyclic antidepressant treatment for children and adolescents with depression failed to produce a replicable pattern of efficacy (March et al., 2004). Until recently SSRIs were recommended because of their relative safety, low lethality on overdose, and ease of administration (Emslie et al., 2002). The Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder recommended using fluoxetine, paroxetine, or sertraline first when medication is warranted for child and adolescent MDD (Emslie et al., 2002). The risk-benefit profile of individual SSRIs has been summarized in an article by Whittington et al. (2004) and more recently in a review by Moreno et al. (2006). Their analysis of published data from four trials of fluoxetine suggested a favorable risk-benefit profile for the treatment of depression in children and young adults; unpublished safety data lent support to this view. Published data from one trial of paroxetine and two unpublished suggested equivocal or weak positive risk-benefit profiles; two trials of Sertraline have been performed; when combining their results there was a small but significant improvement from baseline. Of two trials of Citalopram, of which the positive study was published, one study did not show efficacy, the other showed that the active drug was significantly better than placebo.

But, two trials of venlafaxine and two trials of Mirtazapine suggested unfavorable risk-benefit profiles (Whittington et al., 2004; Moreno et al., 2006). In summary, there seems to be a controversy regarding the efficacy of Fluoxetine but not of other SSRI's in the treatment of pediatric depression. Gibbons et al. (Gibbons et al., 2006) examined the association between antidepressant medication prescription rate and suicide rate in children ages 5-14. They found that higher SSRI prescription rates were associated with lower suicide rates in children and adolescents. Recently evidence was forwarded suggesting that

suicidality, primarily suicidal ideation, in children and adolescents may be increased by the newer antidepressant drugs, primarily selective serotonin-reuptake inhibitors. This raised concerns about the safety of SSRIs; in particular, the possibility that these drugs might be associated with an increased risk of suicidal behavior and that meaningful withdrawal reactions can happen while stopping treatment abruptly. Concerns in the USA about the safety of SSRIs prompted reviews by the US Food and Drug Administration and the American College of Neuropsychopharmacology. The FDA's risk communication began in October 2003 when a public health advisory calling health care professionals' attention to the possibility of an increased risk of suicidality in pediatric patients with depression, who were treated with antidepressant medications. The FDA announcements regarding unpublished efficacy studies suggested that negative results had not been made public. In June 2003, the FDA issued an alert citing uncontrolled studies showing a link between paroxetine treatment and suicide attempts among pediatric patients with depression. In March 2004, the FDA issued a strong warning calling on manufacturers of 10 specific antidepressants, mostly the newer agents, to add to their labeling a warning that all patients (adult and pediatric) being treated with these drugs should be monitored for suicidality. On September 14, 2004, a Food and Drug Administration (FDA) joint advisory committee recommended that a "black-box" warning label be required for antidepressant drugs, indicating that they increase the risk of suicidal thinking and behavior ("suicidality") in pediatric patients. In February 2005, the FDA provided specific language for the warning and required a patient medication guide (Newman, 2004; Libby et al., 2007). The Expert Working Group of the Committee on Safety of Medicines (CSM) undertook upon herself to review of the efficacy and safety of SSRIs in pediatric major depressive disorder. In view of the CSM review, the Medicines and Healthcare products Regulatory Agency (MHRA) released a statement contraindicating the use of all SSRIs other than fluoxetine as new treatment for patients younger than 18 years of age with depressive illness. This advice followed an earlier recommendation by the CSM that both paroxetine and venlafaxine should be contraindicated for use in this context (Emslie et al., 2002; Whittington et al., 2004).

It is worth mentioning that although both these organizations raised concerns about the validity of the suicide data and called for further analyses, neither recommended contraindicating SSRIs (Whittington et al., 2004). Also the above does not address the safety and efficacy for treating other disorders seen in childhood, such as obsessive-compulsive disorder and anxiety with the same drugs (Whittington et al., 2004). In December 2003 The Israel child and adolescent psychiatry association followed the FDA and issued a policy statement similar to that of the FDA, recommending first choice of Fluoxetine or Fluvoxamine for children for whom the treatment with an SSRI is indicated. In a study by Murray et al. (2005) comparing the prevalence and incidence of children and adolescents who were prescribed antidepressants in UK primary care, before and after the UK Committee on Safety of Medicines (CSM) advice on antidepressant prescribing, they found that antidepressant prevalence increased from 2000 to 2002 and from 2002 to 2004 decreased. In this study the prevalence of CSM-contraindicated antidepressants declined by a third, but there was no change in fluoxetine prevalence. Kurdyak et al.

(2007) examined the prescribing trends in Canada in three age groups. They found that the number of new prescriptions for selective serotonin reuptake inhibitors as a group did not change, however, the rate of new Paroxetine prescriptions in patients younger than 20 years declined by 54% immediately after the first warning for Paroxetine was issued in the United Kingdom in June 2003. To our current knowledge no research has been done in Israel regarding the change in utilization of SSRI's following the discussed developments.

2. Methods

2.1 General Aims of the Current Study

The Main aim was to investigate the prescription patterns of antidepressant in the southern region of Israel during the years 2000 to 2005, before and after the FDA blackbox warning issued regarding the prescription of antidepressants in children under 18 years of age. We also wanted to describe prescription pattern of antidepressant drugs according to drug groups during 2000 and 2005. We tried to describe changes in prescribing practice of antidepressant prior to and following the FDA warning.

2.2 Study Hypothesis

We hypothesized, that following the FDA blackbox warning, prescriptions for antidepressant drugs for children less than 18 years of age will be reduced significantly. We thought that the fluoxetine and fluvoxamine were the most prescribe antidepressants as recommended by The Israel child and adolescent psychiatry association.

2.3 Study Type

A cross sectional study was performed. Data regarding prescription of anti depressant drugs was examined retrospectively.

Period: We examined two time periods: from 2000 to 2003, prior to the FDA intervention, and from 2004 to 2005, after the FDA intervention. We measured the % of change in the number of antidepressant type's prescriptions.

Independent variables used were: demographics (age, sex), number and types of antidepressant drugs (SSRI's, Tricyclics, "Other" anti-depressants).

Dependent variable was: The number of prescriptions issued for pediatric patients.

Setting: The Negev region of Israel, a heterogeneously populated area with ~500,000 inhabitants (of whom >190,000 are under 18 years of age) belonging to 2 major ethnicities, Jewish and Moslem Bedouin.

Both groups have similar mental care services provided mainly by the "Clalit Health Care Services", the biggest (55% of market share) health maintenance organization in Israel. Psychiatric healthcare services are provided free of charge and are readily accessible in the community. Medical services are provided by primary care physicians who can prescribe antidepressants following a recommendation given by a board-certified child and adolescent psychiatrist. Six board certified psychiatrics, provide all psychiatric care in the region, treating over 80 percent of children under the age of 18.

Study population: Children under the age of 18, members of Clalit Health Care Services, who had been prescribed antidepressant medication by a primary care physician during the study period. We included all children, for whom the minimum effective dose of medication as defined in our study criteria was purchased. We used a serial number assigned in lieu of an identity number for each patient in order to identify repeat prescriptions.

Data Sources: All information was obtained from the computerized databases of the Clalit Healt care services. The CHS billing system records contains more than 98% of all medical expenditures of the CHCS including all information on issued drugs (type, defined daily dose, number of tablets, and cost for each drug). All prescribed drugs, including antidepressants, are categorized according to the World Health Organization recommendations.

Study protocol:

- First, from the computerized database, of the Clalit Healt care services an inventory of all children under the age of 18 to whom antidepressant drugs were issued.
- Antidepressant drugs were divided into three groups, that were analyzed according to the study variables.

2.4 Study Definitions

- The following groups of antidepressants were defined

Selective serotonin reuptake inhibitors (SSRI's): fluoxetine (flutine, affectine, prozac, prizma), fluvoxamine (favoxil), citalopram (cipramil), paroxetine (paxxet, seroxat), sertraline (lustral)
Noradrenaline reuptake inhibitors: reboxetine (edronax)
Serotonin and noradrenaline reuptake inhibitors: venlafaxine (efexor)
Tricyclic drugs: Amitriptyline (Elatrolet, Elatrol), Clomipramine (Maronil, Anafranil), Imipramine (Primonil, Tofranil), Desipramine (Deprexan), Dibenzepin (Noveril, Victoril), Opipramol (Oprimol).
Other antidepressant medications that are not recommended in children.

- Appropriate treatment was defined as the purchase of a dose of antidepressant medication according to FDA recommendation (Fluoxetine) and Israeli recommendation (Fluoxetine and Fluvoxamine).
- Inappropriate drug treatment was defined as the purchase of antidepressant not according to FDA recommendation medication i.e. all other anti-depressants.

The quality of prescribing did not include dosages or length of treatment because children and adult receive dosages that are the same and not calculated by weight.

Statistical analysis: The data was gathered from the records of the prescriptions. They were coded (to prevent any problems with subjects' confidentiality) and then typed to SPSS statistical software (SPSS 17.0). We analyzed the data first by using descriptive statistics (mean & SD, graphs), and then used analytical statistics using parametric tests: paired t-test, and a-parametric statistics: Mann Whitney & χ^2. When primary analysis showed a significant effect of the use of drugs, we analyzed the data using repeated measurements ANOVA, and it's a-parametric counterpart (The Friedman test).

3. Results

Between the years 2000-2005 a total of 8344 anti-depressant prescriptions were issued for children under the age of 18 (see Table 1). Of these 5845 (70%) were prescriptions for SSRI's, 1644 (19.7%) prescriptions for tricyclics, and 855 (10.2%) for other antidepressants - Moclobemide (1%) (7), Mianserin (1.8%) (16), Milnacepran (2.4%) (20), Mirtazapine (1.1%) (9), Reboxetine (50.3%) (430), Trazadone (2.1%) (18), Venlafaxine (41.5%) (355) (see Table 2).

Table 1. Number of Anti-Depressant Medication Prescriptions Issued during the Years 2000-2005 among Children and Percentage of Change during This Time Period

Year	Nm. of prescriptions[1]	Nm. of patients	Percentage of change	Total Nm. SSRI's [2]
2000	1104	389		613
2001	1104	242	0	707
2002	1301	287	18	976
2003	1492	268	15	1109
2004	1659	317	11	1262
2005	1684	306	2	1178
Total	8344	1809		5845

[1] Nm. of prescriptions issued in the Southern District of Kupat Holim Clalit for all anti-depressant medications to children under the age of 18.

[2] Number of prescriptions issued in the Southern District of Kupat Holim Clalit for all SSRI medications; Fluoxtine (Flutine, Affectine, Prozac, Prizma), Fluvoxamine (Favoxil), Citalopram (Cipramil, Recital), Sertraline (Lustral), Paroxetine (Paroxetine-Teva, Paxxet, Seroxat), Escitalopram (Cipralex)

Table 2. Demographic Data and Number and Type of SSRI Anti-Depressant Medication Prescriptions Issued during the Years 2000-2005 among Children

Year	2000	2001	2002	2003	2004	2005
Nm. of anti-depressant prescriptions[1]	1104	1104	1301	1492	1659	1684
Total Nm. SSRI's	613	707	976	1109	1262	1178
Ratio of total number of anti-depressant prescriptions.	0.56	0.64	0.75	0.74	0.76	0.70
Male/Female Ratio (%) SSRI's[2]	50.6/49.4	51.3/48.7	48.6/51.4	53.7/46.3	54.8/42.2	55.7/44.3
Mean age SSRIs[2]	14.77	14.57	14.96	15.28	15.32	15.02
Nm. "allowed" SSRI's[3]	538	466	447	397	607	615
Male/Female Ratio (%)	49.8/50.2	44.4/55.6	39.1/60.9	48.1/51.9	55.5/44.5	58.4/41.6

"allowed" SSRI's[3]						
Mean age "allowed" SSRI's [3]	14.7	14.08	14.67	15.17	15.07	14.63
Nm. "non-allowed" SSRI's[4]	75	241	529	712	655	563
Male/Female Ratio (%) "non-allowed" SSRI's[4]	56.0/44.0	64.7/35.3	56.5/43.5	56.9/43.1	54.2/45.8	52.8/47.2
Mean age "non-allowed" SSRI's[4]	15.25	15.53	15.21	15.33	15.56	15.45

[1] Nm. of prescriptions issued in the Southern District of Kupat Holim Clalit for all anti-depressant medications to children under the age of 18.

[2] Number of prescriptions issued in the Southern District of Kupat Holim Clalit for all SSRI medications; Fluoxtine (Flutine, Affectine, Prozac, Prizma), Fluvoxamine (Favoxil), Citalopram (Cipramil, Recital), Sertraline (Lustral), Paroxetine (Paroxetine-Teva, Paxxet, Seroxat), Escitalopram (Cipralex)

Of the prescriptions for tricyclic antidepressants 1252 (76.2%) prescriptions were repeated prescriptions. The mean age of the patients who received prescriptions for SSRI's was 15.04 (±2.86). The mean age of the patients who received prescriptions for tricyclics was 12.39 (±3.807).

When comparing the prescription rate of fluoxetine and fluvoxamine versus other SSRI's included in the health agencies warnings during the years mentioned, there was a gradual increase in the percentage of the other SSRI's until 2003 from 12.2% in 2000 to 64.2% in 2003 and then a reversal of this trend from 51.9% in 2004 to 47.8% in 2005 (statistically significant <.001) (see Figure 1).

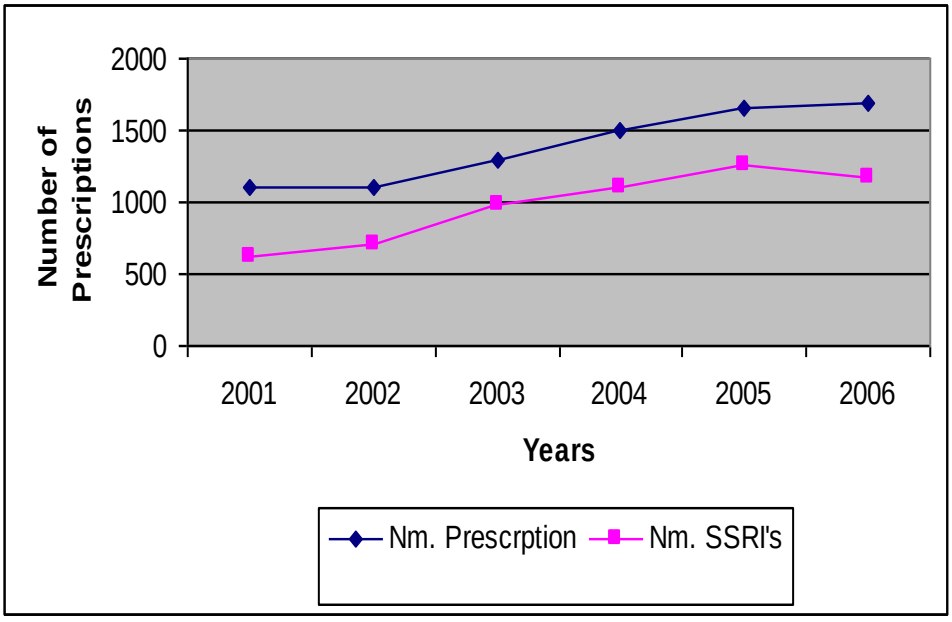

Figure 1. Number of Anti-Depressant Medication Prescriptions Issued during the Years 2000-2006 among Children

There was no difference between the years regarding the prescription rate during different months. Males received 44% of the prescriptions for SSRI's included in the health agencies warning and females 56.0% (statistically significant <.001).

When comparing the years 2003 and 2004 there was a significant difference: 397 prescriptions (35.8%) for favoxil and Fluoxetine and 712 prescriptions (64.2%) for other SSRI's in 2003 versus 607 prescriptions (48.1%) for favoxil and Fluoxetine and 655 prescriptions (51.9%) for other SSRI's in 2004 ($p \leq 0.001$).

When comparing the years 2003 and 2005 there was a significant difference 397 prescriptions (35.8%) for favoxil and Fluoxetine and 712 prescriptions (64.2%) for other SSRI's in 2003 versus 615 prescriptions (52.2%) for favoxil and Fluoxetine and 563 prescriptions (47.8%) for other SSRI's in 2005 ($p \leq 0.001$) .

When comparing the years 2004 and 2005 there was a significant difference: 607 prescriptions (48.1%) for Fluvoxamine (favoxil) and Fluoxetine and 655 prescriptions (51.9%) for other SSRI's in 2004 versus 615 prescriptions (52.2%) for favoxil and Fluoxetine and 563 prescriptions (47.8%) for other SSRI's in 2005 ($p \leq 0.05$).

When comparing the prescription rate of Fluoxetine versus all other SSRI's, as included in the British and American health agencies warnings during the years mentioned, there was a gradual increase in the percentage of the other SSRI's until 2003 from 47.3% in 2000 to 86% in 2003 and then a reversal of this trend from 74.3% in 2004 to 70.8% in 2005.

When comparing the years 2003 and 2004 there was a significant difference: 155 prescriptions (14%) for Fluoxetine and 954 prescriptions (86%) for other SSRI's in 2003 versus 324 prescriptions (25.7%) for Fluoxetine and 938 prescriptions (74.3 %) for other SSRI's in 2004 ($p \leq$ to 0.001). When comparing the years 2003 and 2005 there was a significant difference 155 prescriptions (14%) for Fluoxetine and 954 prescriptions (86%) for other SSRI's in 2003 versus 344 prescriptions (29.2%) for Fluoxetine and 834 prescriptions (70.8%) for other SSRI's in 2005 ($p \leq$ to 0.001). When comparing the years 2004 and 2005 there was not a significant difference: 324 prescriptions (25.7%) for Fluoxetine and 938 prescriptions (74.3%) for other SSRI's in 2004 344 prescriptions (29.2%) for Fluoxetine and 834 prescriptions (70.8%) for other SSRI's in 2005 ($p \leq 0.10$.). When looking at the age of patients subscribed, we can see a steady decrease in age, as is seen in Figure 2.

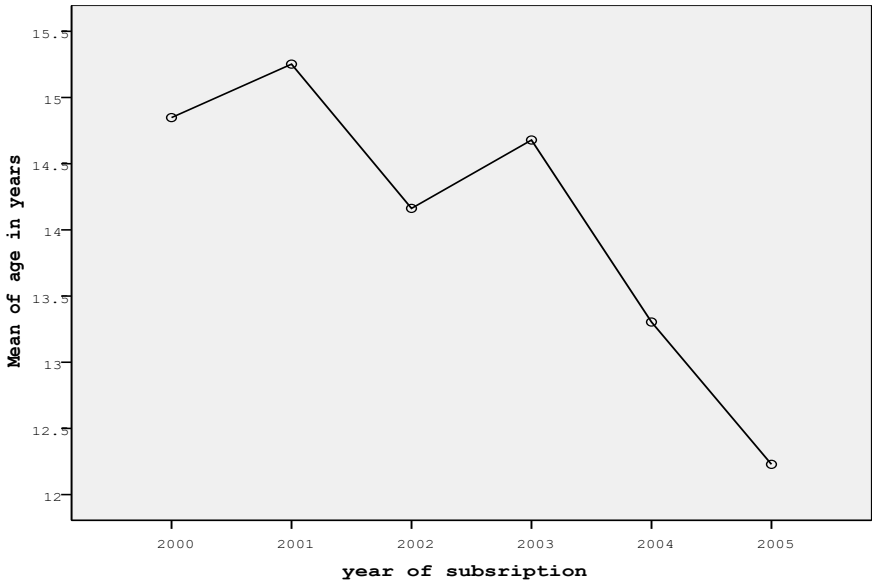

Figure 2. Mean Age of Patients' Subscribed with of Anti-Depressant Medication Issued during the Years 2000-2006 among Children

Summary: During the study period there was a rise in the number of patients prescribed SSRIs. However, from 2003 there was a decrease in prescriptions for CSM-contraindicated antidepressants (Citalopram, Escitalopram, Paroxetine, Sertraline and Venlafaxine). There was an increase in Fluoxetine and Fluvoxamine prescription prevalence. The number of patients prescribed tricyclic antidepressants dropped marginally.

Table 3. Number and Type of Tricyclic Anti-Depressant Medication Prescriptions Issued during the Years 2001-2005 among Children and Demographic Data

Year	Nm. of tricyclics*	Male/Female Ratio (%)-tricyclics*	Mean age- tricyclics*
2000	379	41.4/58.6	12.08
2001	278	38.8/61.2	12.94
2002	251	44.2/55.8	12.43
2003	246	42.7/57.3	11.43
2004	229	50.2/49.8	12.65
2005	261	43.3/56.7	12.9
Total	1644		

* Number of prescriptions issued in the Southern District of Kupat Holim Clalit for all tricyclic medications; Clomipramine (Anafranil, Maronil), Desipramine (Deprexan), Amitriptyline (Elatrol, Elatrolet)

Doxapine (Gilex), Imipramine (Primonil, Tofranil), Maprotiline (Melodil), Nortriptyline (Nortylin)

Table 4. Number and Type of "Other" Anti-Depressant Medication Prescriptions Issued during the Years 2001-2005 among Children and Demographic Data

Year	Nm. "other" anti-depressants*	Male/Female Ratio (%)-"other" anti-depressants*	Mean age- "other" anti-depressants*
2000	112	59.8/40.2	14.85
2001	119	41.2/58.8	15.25
2002	74	28.4/71.6	14.16
2003	137	48.2/51.8	14.68
2004	168	25/75	13.3
2005	245	24.5/75.5	12.23
Total	855		

* Moclobemide (Mobemide), Mianserin (Bonserin), Reboxetine (Edronax), Ixel, Mirtazapine (Remeron, Miro) Trazodone (Trazodil, Trittico, Depyrel) Venflaxine (Efexor, Venla, Viepax)

[1] Nm. of prescriptions issued in the Southern District of Kupat Holim Clalit for all anti-depressant medications to children under the age of 18.

[2] Number of prescriptions issued in the Southern District of Kupat Holim Clalit for all tricyclic medications; Clomipramine (Anafranil, Maronil), Desipramine (Deprexan), Amitriptyline (Elatrol, Elatrolet)

Doxapine (Gilex), Imipramine (Primonil, Tofranil), Maprotiline (Melodil), Nortriptyline (Nortylin)

Table 5. Demographic Data and Number and Type of "Other" Anti-Depressant Medication Prescriptions Issued during the Years 2000-2005 among Children

Year	Nm. of prescriptions[1]	Nm. "other" anti-depressants[2]	Ratio of total number of anti-depressant prescriptions	Male/Female Ratio (%)-"other" anti-depressants[2]	Mean age- "other" anti-depressants[2]
2000	1104	112	0.1	59.8/40.2	14.85
2001	1104	119	0.1	41.2/58.8	15.25
2002	1301	74	0.05	28.4/71.6	14.16
2003	1492	137	0.09	48.2/51.8	14.68
2004	1659	168	0.1	25/75	13.3
2005	1684	245	0.14	24.5/75.5	12.23
Total	8344	855	*0.1	**	***

[1] Nm. of prescriptions issued in the Southern District of Kupat Holim Clalit for all anti-depressant medications to children under the age of 18.

[2] Moclobemide (Mobemide), Mianserin (Bonserin), Reboxetine (Edronax), Ixel, Mirtazapine (Remeron, Miro) Trazodone (Trazodil, Trittico, Depyrel) Venflaxine (Efexor, Venla, Viepax)

* $\chi^2 = 65.5$, df = 5, $p<0.001$; ** $\chi^2 = 43.9$, df = 5, $p<0.001$; $F(5,849)= 21.12$, $p<0.001$ ***

4. Discussion

Depression is a serious condition, associated with considerable morbidity and mortality; selective serotonin reuptake inhibitors (SSRIs) were commonly used in its treatment in child and adolescent psychiatry with increased prevalence until 2003. Our study shows that this is also true in the Negev Region of Israel, with increased use of SSRI's other than Fluoxetine. In the wake of the UK Committee on Safety of Medicines (CSM) advice and the FDA's issued black box warning, several studies attempted to review and study the connection between SSRIs and suicidality in children and adolescents. The findings were confusing and are insufficient at this time. There is insufficient safety information from randomized controlled trials to confirm a definite association between SSRIs and suicidality. We examined the prescribing practice regarding anti depressants especially SSRI's in light of the current controversy over SSRI prescribing. Our study indicated that there has not been a decrease in prescriptions for children and adolescents. However, there has been a change in the choice of an SSRI. We conclude that even though there is still controversy as to whether there is indeed an increased risk of suicidality following treatment with anti-depressants in children and adolescents, physicians continue to treat depressive episodes with anti-depressants. This may be due to the fact that many of the prescriptions are prescribed directly by family physicians and are not based on a recommendation by a child psychiatrist, in which case the family physicians may be less aware of the above-mentioned warning. Were this true, however, there would probably have been no change at all in the prescribing trends which was not the case.

There may also not be a reduction in the number of prescriptions issued due to a lack of available services and a paucity of therapists trained in evidence-based psychotherapies. The effect of the warnings on prescription rates may have occurred by directly targeting physicians or through change in client preference due to exposure of patients to information through the media.

Our study points to the impact of change in policy by Regulatory agencies and shows that changes in policy can influence common practice even when the recommendation or warning is controversial and the evidence upon which it is based is debatable.

Limitations of the study: Due to the use of the Kupat Holim Clalit data-base on the basis of prescribing information without accessing the patients' files, we do not have information regarding diagnosis.

One must remember that this is a retrospective study, and thus our ability to talk about causality is hampered.

We did not interview physicians themselves and thus our results are based on assumptions which are logical but lack the insight from the prescribing physicians.

Future studies: Further studies are needed to address whether the change we found in prescribing of anti-depressants is influenced by the child's diagnosis and whether different anti-depressants are prescribed for diagnosis other than depression.

Also, future studies need to address the factors taken into consideration when prescribing anti-depressive medication.

In addition, more studies are needed in order to examine whether indeed there has been a change in youth suicidality following the change in anti-depressant prescribing.

5. Conclusions

In our study we found an increase in antidepressant use over the years. Examining the prescription trend from 2000 we found that until 2003 there was an increase in the use of all SSRI's. Since 2003, fewer children and adolescents have been prescribed antidepressants included in the CMS warnings. However in contrast to the study performed by Murray et al (Murray et al., 2005) we did find an increase in the use of fluoxetine and fluvoxamine. These medications were considered first choice treatments according to the recommendation issued by The Israel child and adolescent psychiatry association. This study shows that the CSM advice has not had a significant effect in reversing the rising prevalence of antidepressant prescribed to children and adolescents in primary care. It has however changed the choice of antidepressant medication chosen within the group of SSRI's. Considering that the mean age for tricyclic prescriptions was approximately 2 years younger than that for SSRI's, we can hypothesize that tricylics were prescribed for enuresis and not for depression. There is a slight decrease in prescription of tricyclics which does not seem to be significant indicating that physicians have chosen not to prescribe tricyclic medication as an alternative to SSRI's.

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