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Suicidal risk from TADS study was higher than it first appeared

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Abstract. Completed suicides are a major cause of death in adolescents in Sweden. Forensic analysis of completed suicides in children and adolescents shows there is one completed suicide per 1000 children taking a selective serotonin re-uptake inhibitor (SSRI). In order to elucidate these events we undertook a study of the results and reporting of suicidal events in the Treatment of Adolescents with Depression Study (TADS). We conclude that a major, albeit underreported, finding in the TADS was the significant increase of suicidal events in the adolescents on antidepressant medication in comparison to the group on placebo medication. The proportions of suicidal events were 11% and 2.7% respectively. This increased risk of suicidal events might be related to the high incidence of medication with an SSRI in the group of completed suicides among Swedish adolescents.

Keywords: SSRIs, suicide, adolescent depression, TADS, CBT

1. Introduction

There have been multiple meta-analyses focusing on the risk of increased suicidality in SSRI-treated adolescents. Dubicka et al. analysed 15 studies with SSRIs and young people diagnosed with depression [1]. They found that suicide attempts and self-harm occurred more frequently in the SSRI-treated group compared with the placebo group (fixed effects odds ratio 1.70, 95% CI, 1.13–2.54, $P = 0.01$). Hammad et al. included 16 pediatric SSRI studies with the diagnostic category of depression [2]. The increased risk for those treated with SSRIs compared with those treated with placebo was 1.66 (95% CI, 1.02–2.68). The conclusion was that "Use of antidepressant drugs in pediatric patients is associated with a modestly increased risk of suicidality". Bridge et al. in a meta-analysis of 27 pediatric studies with SSRIs in different clinical conditions found an increased risk difference of suicidal ideation/suicide attempt in all

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trials (0.7%; 95% CI, 0.1% to 1.3%), the number needed to harm was 143, thus there were 0.7% suicidal events with an antidepressant [3]. Finally, in a matched case-control study, Olfson et al. found a significant increased risk with antidepressant drugs in children and adolescents regarding suicide attempts (OR, 1.52; 95% CI, 1.12–2.07), and completed suicides (OR, 15.62; 95% CI, 1.65-infinity) [4].

Individual studies vary in how they measure suicidality. Suicidality is usually not reported as an outcome measure but rather as a spontaneously reported adverse event. Suicides are usually not classified based on a systematic assessment. Studies also evaluate different types of SSRIs. All of these factors make it difficult to compare across studies.

In this short report we aim to better understand the relationship between a prescription of an SSRI and completed suicide in children and adolescents in Sweden. In the USA and in Europe the only SSRI approved for administration to depressed children and adolescents is fluoxetine. We chose to analyse the findings and reporting on suicidality related to fluoxetine. Because the Treatment of Adolescents with Depression Study (TADS) systematically analysed adverse reactions for suicidal events during the trial, we chose to examine the results and the presentations of the suicidal events data from TADS.

2. Methods

We selected and closely scrutinized the publications from TADS presenting the clinical results, including aspects of safety. We studied those articles and compared the presentation of their findings regarding suicidal events in the abstracts of the articles with the actual results.

3. Results

Although TADS did not have a separate reporting of suicidal events, these data were included among the adverse events reported by patients and parents. These events were reviewed and coded by the Columbia Classification Algorithm of Suicidal Assessment (C-CASA). The C-CASA is a retrospective Columbia suicide severity rating scale (C-SSRS). The coding was done independently by the Columbia University Suicidality Classification group [5]. The concept "suicidal event" consisted of "...discrete episodes of suicidal ideation, suicidal attempts, or preparatory acts toward an imminent attempt" [6]. Self-injury without suicidal intent was not registered as a suicidal event.

In TADS, 439 depressed youths were randomly assigned to four treatment arms. These were placebo (PBO, $n = 112$), fluoxetine only (FLX, $n = 109$), cognitive behaviour therapy only (CBT, $n = 111$), or a combination of cognitive behaviour therapy and fluoxetine (COMB, $n = 107$). These four groups underwent a randomized controlled trial (RCT) over 12 weeks, with an open continuation follow-up until week 36 of the study. During the follow-up, several former PBO subjects switched to active treatment with FLX or COMB [7]. The suicidal events during the study were depicted as in Fig. 1 from Vitiello et al. [6].

In Fig. 1, based on the original figure from Vitiello et al., the total number of suicidal events in FLX and COMB are shown as black symbols [6] while empty symbols are suicidal events without fluoxetine in the PBO and CBT groups. There were 44 subjects with at least one suicidal event during the 36 study weeks, and of these, 55% were hospitalized. Based on the data depicted in Vitiello et al., these researchers concluded that the percentage of suicidal events was 14.7% ($n = 16$) with fluoxetine only and 10.7% ($n = 12$) with placebo, a non-significant difference. However, it is of note that of those 12 placebo cases, 9 subjects were in fact taking fluoxetine medication, i.e., there were only three subjects taking

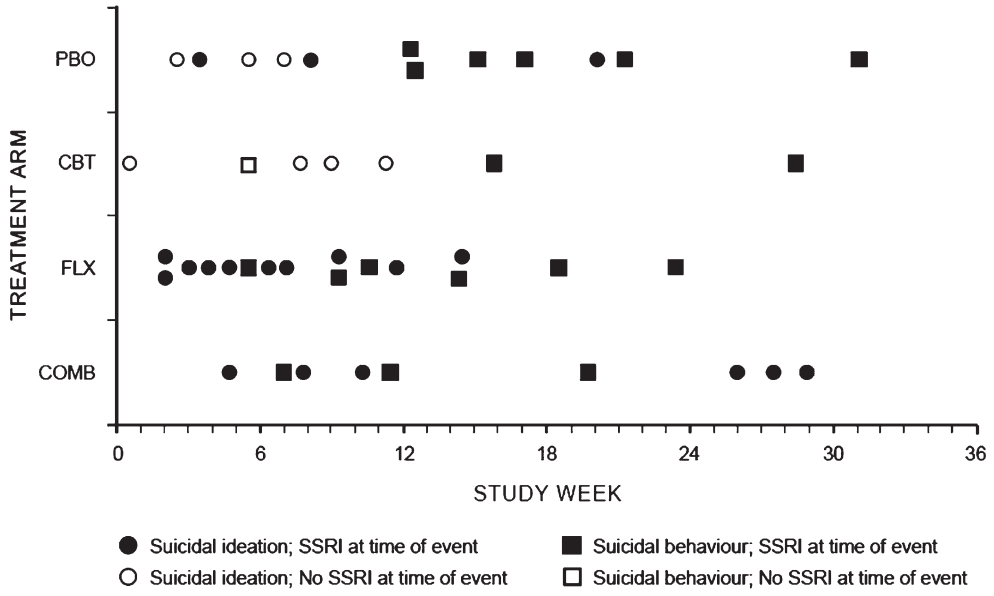

Fig. 1. Circles represent suicidal ideation and squares represent suicide attempts. Black filled symbols are subjects on fluoxetine and open symbols are subjects on placebo or cognitive behavioural therapy.

Table 1
The 12 week comparison among PBO, FLX, CBT and COMB concerning suicidal events

Treatment	*n*	Subjects with a suicidal event	%	Significance Fisher's exact test 2-tailed
PBO	112	3	2.7	
FLX	109	12	11	$p = 0.016$
COMB	107	5	4.7	ns
CBT	111	5	4.5	ns

placebo who had a suicidal event. In a table footnote, the authors reported a significantly higher level of suicidal events on FLX when compared with the CBT only and PBO patients who were not actually taking medication. They also found that there was a significant relationship between high pre-treatment scores on the self-administered depression questionnaire (the Reynolds Adolescent Depression Scale) and the emergence of suicidal events. Another important finding was that the suicidal events were not necessarily preceded by clinical deterioration or behavioural activation. Regarding homicidal ideation, two subjects treated with fluoxetine had an episode of increased homicidality [8].

However, alerted by this table footnote [6], we changed the classification of the two subjects on SSRI in the placebo group as they could not be reasonably classified as placebo at the time of the suicidal event (Fig. 2). The numbers and percentages of suicidal events associated with each treatment during the 12 weeks are shown in Table 1. The significance of the differences in proportion of youths with suicidal events between the placebo group and the other groups was calculated with Fisher's exact test, two-tailed, and the significance threshold was set at 0.05.

Table 2
Reporting of suicidality in the *TADS abstracts*

Title, year	Reporting on suicidality in the abstracts for the different treatment arms	Comment
Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression, 2004 [9]	"Clinically significant suicidal thinking, which was present in 29% of the sample at baseline, improved significantly in all 4 treatments groups"	This does not report the significantly higher rate of suicidal events in the fluoxetine group compared with placebo
Treatment for adolescent with depression study (TADS): safety results, 2006 [8]	" Statistically, only FLX had more suicide-related events than PBO"... "In this study, psychiatric AEs and suicide-related events are more common in FLX-treated patients"	This was a correct reporting although it did not mention that the difference regarding suicidal events was statistically significant
The treatment for adolescents with depression study (TADS): methods and message at 12 weeks, 2006 [10]	"Despite the fact that suicidality improved markedly across all of the treatment conditions, suicidal events were twice as common in patients treated with FLX alone than with COMB or CBT alone, perhaps indicating that CBT protects against suicidal events"	There was an omission of the fact that there was a significantly higher rate of suicidal events in the fluoxetine group compared to the placebo group
The treatment for adolescents with depression study (TADS) long-term effectiveness and safety outcomes, 2007 [11]	"Suicidal events were more common in patients receiving fluoxetine therapy (14.7%) than combination therapy (8.4%) or CBT (6.3%)"	There was an omission of the placebo group and the significantly higher rate of suicidal events in the fluoxetine group
Assessment of safety and long-term outcomes of initial treatments with placebo in TADS, 2009 [7]	"There were no differences between groups in rates of suicidal events, study retention, or symptom worsening"	This statement was not in accordance with the results showing 17 suicidal events in the group taking fluoxetine between 12 and 36 weeks and none in the CBT or placebo group
Suicidal events in the treatment for adolescents with depression study, 2009 (TADS) [6]	"Forty-four patients (10.0%) had at least one suicidal event (no suicide occurred)"	There was no comment on the difference between treatment arms. The following note about suicidal events with fluoxetine in table 1 was not mentioned in the abstract: "Higher than in CBT ($p = 0.04$) or PBO ($p = 0.02$), when considering only the CBT and PBO patients who were not on medication at time of the event"
Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the TADS randomized trial, 2009 [12]	" . . . the cost of services received outside Treatment of Adolesents with Depression Study in fluoxetine-treated patients (mean $ 5,382, median $ 2,341) were significantly higher than those participants treated with cognitive-behavioral therapy(mean $3,102, median $1,373) . . . "	The authors did not mention that this increased cost was from psychiatric hospital use related to suicidal events

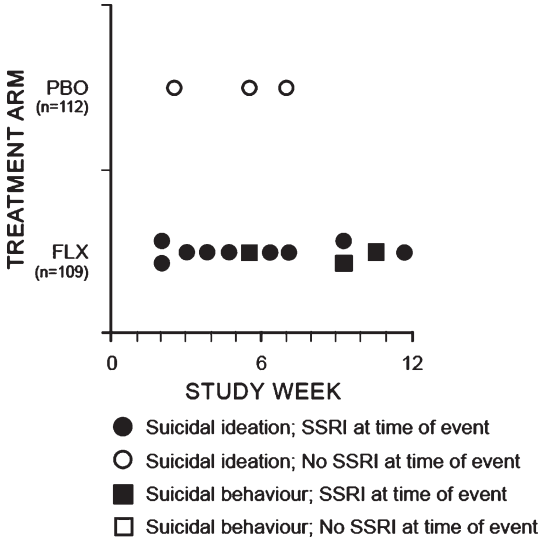

Fig. 2. Circles represent suicidal ideation and squares represent suicide attempts. Black filled symbols are subjects on fluoxetine and open symbols are subjects on placebo.

The analysis of the data showed that there was a statistically significant difference in proportion of youths with suicidal events between the PBO condition (2.7%) and the FLX treatment (11%) during the 12 weeks of treatment. After 12 weeks of the randomized controlled trial, several PBO participants started treatment with FLX or COMB for the last 24 weeks of the study. Over these 24 weeks there were 17 suicidal events, all of them in subjects taking SSRI (Fig. 1). What we also did note was that the suicidal events in the study were evenly distributed over the entire time period; thus highlighting that the risk for suicidal events in SSRI-treated adolescents appears to be increased up to eight months after the start of medication.

None of the seven abstracts from TADS publications mentioned the fact that there were four times more suicidal events with fluoxetine than with placebo during the randomized controlled trial, and that this difference was statistically significant (Table 2).

4. Discussion

The findings of SSRI-related increased suicidality in TADS underlines the need for specific monitoring of suicidality in studies on depressed adolescents. The Columbia Suicide Severity Rating Scale, which measures both suicidal ideation and suicide attempts, is a promising tool for such standardised observation [5]. Antidepressant induced violent behaviour is serious enough to also warrant standardised assessment. We suggest that a similar scale should be developed for homicidality, measuring both homicidal ideation and homicidal acts.

A hypothetical mechanism for the increased suicidality in adolescents taking SSRIs could be a disruption of affect regulation with ensuing lack of constraints on suicidal impulses. Negative affective states in adolescents treated with an SSRI have for instance been described as “amotivational syndrome” by Garland and Baerg and as “selective serotonin reuptake inhibitor-induced apathy” by Reinblatt and Riddle [13, 14]. A similar effect of anhedonia with SSRI-treatment has been described by Price, Victoria, and

Goodwin [15]. Another study on 1829 adult subjects receiving SSRI-treatment found that 60% reported emotional numbness as a side-effect [16]. This "care less syndrome" might diminish the empathy with others that functions as a hindrance to acting on suicidal impulses. It might also create a state of emptiness and lifelessness that can become unbearable to the young person. Finally a potential mechanism for an SSRI induced suicidal event could be the reported risk of pathological intoxication, amnesia and loss of impulse-control, with moderate doses of alcohol combined with an SSRI [17].

TADS neglected to report in the abstracts the finding of a significantly higher rate of suicidal events with fluoxetine compared with placebo. The omission of an important negative clinical outcome from any study is not in the interest of patients or clinicians who are trying to practice evidence based medicine. We suggest for future publications that reviewers and publishers examine more closely the congruence between findings and abstracts.

The findings of completed suicides on SSRI-medication in Swedish adolescents may be relevant to the reported increased risk with SSRI in adolescents. In the reported forensic examination of completed suicides (2006–2010) by adolescents in Sweden a selective serotonin reuptake inhibitor (SSRI) was found in the blood of adolescent patients from 42 suicides, 14% of completed suicides [18]. During the same period 40,437 children age 10–19 were prescribed a SSRI [19]. From these figures one can calculate a rate of 0.1 per cent (1/1000) completed suicides in children and adolescents prescribed a SSRI as noted by the Swedish National Board of Health and Welfare. The suicide rate in Sweden in this age group is about 4/100,000 persons. The relative risk of completed suicide in a clinical sample with an SSRI in this age group is thus about 25.

In summary, the data from Sweden showed that there was a high proportion of SSRI medication in completed suicides among patients in treatment. TADS showed there was a significant increase in suicidal events with fluoxetine, that the risk remained high during the entire treatment period, that the increased suicidality was associated with higher intake scores in self-evaluated depression, and that there were no identified clinical signs indicating the risk for a suicidal event. This increased risk of suicidal events with SSRI in TADS may help us understand the observed completed SSRI-related suicides in Swedish adolescents. These data from TADS are important for regulatory agencies on drug safety. It is imperative that the vigilance system for adverse drug effects considers and registers suicidal events with SSRIs as possible adverse side effects. Also it is crucially important that depressed youth taking SSRIs be closely monitored throughout the duration of treatment.

References

[1] Dubicka B, Hadley S, Roberts C. Suicidal behaviour in youths with depression treated with new-generation antidepressants. Br J Psychiatry. 2006;189:393-98.

[2] Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006;63:332-39.

[3] Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment, a meta-analysis of randomized controlled trials. JAMA. 2007;297(15):1683-96.

[4] Olfson M, Marcus SC, Schaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults. Arch Gen Psychiatry 2006;63:865-72.

[5] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia classification algorithm of suicide assessment (C-CASA). Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-43.

[6] Vitiello B, S. Silva S, Rohde P, Kratochvil CJ, Kennard B, Reinecke M, Mayes TL, Posner K, May DE, March JS. Suicidal events in the treatment for adolescents with depression study (TADS). J Clin Psychiatry. 2009;70(5):741-47.

[7] Kennard BD, Silva SG, Mayes TL, Rohde P, Hughes JL, Vitiello B, Kratochvil CJ, Curry JF, Emslie GJ, Reinecke MA, March JS. Assessment of safety and long-term outcomes of initial treatment with placebo in TADS. Am J Psychiatry. 2009;166(3):337-44. doi: 10.1176/appi.ajp.2008.08040487
[8] Emslie GJ, Kratochvil C, Vitiello B, Silva S, Mayes T, McNulty S, Weller E, Waslick B, Casat C, Walkup J, Pathak S, Rohde P, Posner K, March J. Columbia suicidality classification group, and the TADS team. Treatment for Adolescents with Depression Study (TADS): Safety results. J Am Acad Child Adolesc Psychiatry. 2006;45(12):1440-54.
[9] March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial, JAMA. 2004;292(7):807-20.
[10] March J, Silva S, Vitiello B, and the TADS team. The treatment for adolescents with depression study (TADS): Methods and message at 12 weeks. J Am Acad Child Adolesc Psychiatry. 2006;45:1393-403.
[11] March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. The treatment for adolescents with depression study (TADS): Long-term effectiveness and safety outcomes. Arch Gen Psychiatry. 2007;64(10):1132-44.
[12] Domino EM, Foster EM, Vitiello B, Kratochvil CJ, Burns BJ, Silva SG, Reinecke MA, March JS. Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the TADS randomized trial. J Am Acad Child Adolesc Psychiatry. 2009; 48(7):711-20. doi: 10.1097/CHI.0b013e3181a2b319
[13] Garland EJ, Baerg AA. Case report, amotivational syndrome associated with selective serotonin reuptake inhibitors in children and Adolescents. J Child Adolesc Psychopharmacol. 2001;11(2):181-201.
[14] Reinblatt SP, Riddle MA. Selective serotonin reuptake-inhibitor-induced apathy: A pediatric case series. J Am Acad Child Adolesc Psychiatry. 2006;16(1/2):227-33.
[15] Price J, Cole V, Goodwin GM. Emotional side-effects of selective serotonin reuptake inhibitors: Qualitative study. Br J Psychiatry. 2009;195:211-17.
[16] Read J, Cartwright C, Gibson K. Adverse emotional and interpersonal effects reported by 1829 New Zealanders while taking antidepressants. Psychiatry Res. 2014;216:67-73.
[17] Herxheimer. Violence as a side-effect of antidepressants: Provocation by alcohol. P-10-004, Abstracts of the 9th World Congress of Biological Psychiatry, Paris: 2009.
[18] Isacsson G, Ahlner J. Antidepressants and the risk of suicide in young persons – prescription trends and toxicological analyses. Acta Psychiatr Scand. 2014;129(4):296-302. DOI: 10.1111/acps.12160
[19] Swedish national board of health and welfare. www.socialstyrelsen.se/statistik/statistikdatabas