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Critical appraisal of adverse effects reporting in the "Treatment for Adolescents With Depression Study (TADS)" study

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Abstract

Objective To identify all publications from the "Treatment for Adolescents With Depression Study (TADS)" study and assess the findings regarding occurrence of any adverse effects in the treatment groups both for the short-term and long-term study stages.

Design Descriptive analysis of TADS study publications with any information on adverse effects.

Results We identified 48 publications describing various aspects of the TADS study, in which 439 adolescent patients received treatment with fluoxetine, cognitive behavioural therapy (CBT), cognitive behavioural therapy plus fluoxetine, or placebo. Eight publications were assessed as providing some data on adverse effects. Risk of suicidal behaviour was the only adverse effect that was addressed in all publications. Several psychiatric and physical adverse effects were reported during the first 12 weeks, but not mentioned in reports from later study stages. Common adverse effects of fluoxetine, such as weight changes or sexual problems, were not identified or mentioned in the publications.

Conclusions The TADS study publications do not present a comprehensive assessment of treatment risk with fluoxetine in adolescents, especially for more than 12 weeks of treatment. Risk of suicidality was the only adverse effect that was reported over time. Reporting of adverse effects was incomplete with regard to the long-term safety profile of fluoxetine.

Strengths and limitations of this study

- This is the first systematic assessment of adverse effects reporting in publications from the TADS study.
- The analysis encompasses all adverse events mentioned in publications from the TADS study.
- An extensive literature search was conducted and we believe that all relevant studies have been identified
- We cannot exclude the possibility that some publications may have been overlooked.

Critical appraisal of adverse effects reporting in the "Treatment for Adolescents With Depression Study (TADS)" study

Introduction

In 1998, the US National Institute of Mental Health (NIMH) issued a request for proposals (RFP-NIH-NIMH 98-DS-0008) with the objective of launching a clinical trial to address the effectiveness of treatment for adolescents with major depression.[1] The subsequent study, "Treatment for Adolescents With Depression Study (TADS)" was coordinated by the Department of Psychiatry and Behavioral Sciences and the Duke Clinical Research Institute, both at Duke University Medical Center, collaborating with and funded by NIMH,[2] and carried out in the period 2000-2003.[3] The study included 439 youths who were randomized to one of four treatment groups; 1) fluoxetine (FLX), 2) cognitive behavioural therapy (CBT), 3) cognitive behavioural therapy plus fluoxetine (COMB), or 4) placebo (PBO) for twelve weeks (stage I).[3] Double blind treatment was performed among patients treated with fluoxetine and placebo only, while patients treated with CBT with or without fluoxetine received open treatment. Stage II and III were maintenance phases for the active treatment groups, with the option of intensifying treatment for partial responders. Patients in the placebo group were offered open active treatment of fluoxetine, CBT or both. Stage IV consisted of an additional year of open follow-up.[2]

The two primary outcome measures in the TADS study were Children's Depression Rating Scale-Revised (CDRS-R) total scores, and responder status on the Clinical Global Impressions-Improvement (CGI-I) scale. According to protocol, all analyses would be performed by intention to treat (ITT), regardless of later events.

Adverse events during the acute and maintenance phases were defined as secondary outcomes.[4] Patients were monitored for safety regarding affective disorders, need for mental health treatment, need for concomitant medications, occurrence of adverse events and serious adverse events, and use of adjunctive services and attrition prevention (ASAP). Most assessments were based on both patient and parent information.[5]

The TADS study has been described as the largest and arguably the highest-quality acute-phase randomized placebo controlled trial of an antidepressant drug for adolescent depression[6] and is one of two clinical trials of fluoxetine included for risk/benefit assessment in the latest Cochrane systematic review of antidepressant treatment in children and adolescents.[7] We understand from the protocol and monitoring procedures that the TADS study team intended to evaluate the tolerability of treatment, and that the study was expected to provide improved insight into the potential adverse effects of antidepressant treatment in this age group, due to its study size and duration. Several publications from the TADS study have addressed risks of adverse effects. Despite this, concerns have been raised regarding underreporting of suicidal risk,[8] study size and an increased risk of psychiatric adverse effects.[9]

In the TADS study, adverse events were defined as an unfavorable medical change that occurred after beginning or during the study that might or might not be related to or caused by the study drug or CBT treatment. This was further specified as any medical event that caused clinically significant interference with functioning, any event that required medical attention, and any medical event associated with impairment in functioning and induced the patient to take a concomitant medication. Conditions that did not lead to clinically significant interference with functioning or did not require medical attention were not defined as adverse events.[4] The

protocol specified that new onset psychiatric symptoms such as emerging mania or panic attacks would be recorded if they caused clinically significant interference with functioning.[5] It follows that such conditions would not be recorded unless a certain severity threshold was reached.

Harm-related adverse events were defined as involving harm to self, which could include a non-suicidal event. Examples given are cutting, worsening of suicidal ideation, suicide attempt or harm to others. Suicide-related adverse events were defined as worsening suicidal ideation and/or suicide attempt. Adverse Event Forms were to be used throughout the study and it must be assumed that such data were collected, as well as clinical scoring data for possible psychiatric adverse events.

The Norwegian Regional Medicines Information & Pharmacovigilance Centres (RELIS) and the Centre for Psychopharmacology at Diakonhjemmet Hospital regularly receive queries from hospital doctors and general practitioners regarding the safety of fluoxetine and other selective serotonin reuptake inhibitors in adolescent patients. Our objective in the present study was to identify all publications from the TADS study and assess the findings regarding occurrence of any adverse effects in the treatment groups both for the short-term and long-term study stages. The TADS study was chosen because of the non-industrial funding and because it is considered as a high-quality study.[6]

Method

Publications from the TADS study were identified through searches in PubMed, EMBASE, Psychinfo, Google Scholar, clinicaltrials.gov, by hand searching of references in identified publications, and by searching other publications by the main authors. Identified TADS publications were assessed and classified according to publication topic and reported outcomes. Publications describing any adverse events during treatment were analyzed in detail regarding the types and frequency estimates of adverse events. Two researchers (TW and SN) evaluated each publication independently.

Results

We identified 48 publications that reported on the study protocol and/or various outcomes in the TAD study population. The selection process and publication characteristics are described in figure 1.

Eight publications were assessed as providing at least some data on adverse effects,[3 10-16] of which four publications reported possible adverse effects for subgroups of patients only; patients who responded to treatment,[11] patients originally assigned to PBO treatment,[14] patients who had at least one suicidal event,[15] and patients using attrition prevention services,[12] respectively. Reporting of adverse effects was most detailed in the two initial results publications from stage I (0-12 weeks),[3 10] and included a wide range of adverse effects, including several psychiatric and gastrointestinal reactions. One stage I publication did not address adverse effects explicitly; however, symptoms that may be associated with adverse effects were described as residual symptoms of depression.[11]

The publications that reported on adverse effects in the later study stages II, III, and IV listed few adverse effects except suicidal behaviour (table 1). The publication that purported to report on long-term effectiveness and safety outcomes only included reporting of suicide-related adverse events.[13]

Table 1 Reporting of adverse events in publications from the TADS study†

	Stage 1 (12 weeks)				Stage 2+3 (36 weeks)			Stage 4 (88 weeks)
Reported event	TADS[3]	Emslie[10]	Kennard[11]α	May[12]β	TADS[13]	Kennard[14]γ	Vitiello[15]δ	TADS[16]
Harm-related adverse event	x	x		x				
Suicide-related adverse event	x	x	x *	x	x	x	x	x
Attempted suicide	x	x		x	x	x	x	
Homicidality		x		x				
Mania	x	x		x			x	
Hypomania	x	x		x				
Elevated mood	x	x						
Trouble attention/concentration		x	x *					
Racing thoughts		x						
Excessive talking/talking very fast		x						
Increase in activities		x						
Impulsivity		x						
Hypersensitivity **	x	x						
Irritability	x	x	x *				x	
Anger	x	x						
Worsening of depression	x	x		x		x	x	x
Psychomotor			x *					
Guilt			x *					
Mood			x *					
Interest			x *					
Crying	x	x						
Agitation	x	x						
Akathisia	x	x						
Nervousness	x	x						
Restlessness	x	x						
Hyperactivity	x	x						
Panic attacks	x	x						
Anxiety	x	x						
Excessive sweating		x						
Difficulty breathing		x						
Hearing problems		x						
Somnolence/feeling drowsy	x	x						
Insomnia/sleeplessness	x	x					x	
Sleep	x	x	x *					
Nightmare	x	x						
Night sweats	x							
Sedation	x	x						
Fatigue	x		x *					
Tremor	x	x						
Behaviour/feeling abnormal	x	x						
Social problems				x			x	
Headache	x	x						
Upper abdominal pain	x	x						
Stomach pain		x						
Diarrhea	x	x						
Influenza/sinusitis	x							
Cold, sore throat, cough/wheez		x						
Allergies		x						
Dry mouth		x						
Nausea/vomiting	x	x						
Fever		x						
Muscle aches or cramps		x						
Joint pain		x						
Numbness or tingling arms or legs		x						
Weight			x *					
Chest pain		x						
Racing/pounding heart, skip beats		x						
Urination frequency or pain		x						
Constipation, feeling bloated		x						
Skin rash/hives		x						

† Relationship with treatment not established
α Reporting limited to responders subgroup, regardless of treatment arm
β Reporting limited to subgroup of patients seeking attrition prevention
γ Reporting limited to ITT placebo group
δ Reporting limited to patients with a suicidal event
* Reported as residual symptoms of depression
** Understood as mood hypersensitivity

Patient population and treatment modifications during the study

In the TADS study, 439 patients were randomized to one of the four treatment groups. By the end of stage I (12 weeks), 351 patients remained for assessment, of them 270 patients in active treatment groups. The rest of the patients had either withdrawn their consent, or been classified as premature terminators due to need for additional treatment.[3 13] It is not clear to what extent this affected the inclusion of adverse effects that caused discontinuation or drop-out, or occurred after treatment termination. By week 36 (end of stage III), 178 patients remained in the group to which they had been randomized, specifically 68 for COMB, 55 for FLX and 55 for CBT.[13] Patients who terminated their assigned treatment prematurely did in many cases continue their assessments and were included in the ITT analyses for their original group, although they received an active treatment other than that specified for the group they were assigned to.[10 13 17] Between 34 and 46% of patients in the monotherapy groups did not remain in their assigned treatment arm by the end of stage II, and 43 of the 111 patients (38%) in the CBT group were receiving another SSRI or antidepressant by the end of stage III (36 weeks).[17]

Reporting of suicidality in TADS publications

Suicidality symptoms were monitored using an affective disorders screening procedure (ADS), Reynolds adolescent depression scale (RADS), a revised Children's Depression Rating Scale (CDRS-R), a Suicide Ideation Questionnaire (SIQ-Jr) as well as adverse event/serious adverse event forms. All the TADS publications classified as reporting adverse effects [3 10-16] describe the risk of suicidal events, defined as discrete episodes of suicidal ideation, suicidal attempts, or preparatory acts toward an imminent attempt. Injury to self was not included if there was no suicidal intent. Reporting of suicidal events and -risk is described in the supplementary file. Data on suicidality are presented as either counts of discrete episodes, mean scores, score changes or proportion of patients reaching threshold values on scoring tools.

By week 12, CDRS-R item 13 scores are reported as percent of patients with score ≥ 2 for the total study population,[3] percent of patients with score worsening ≥ 1 point, and percent of patients with score increase from 1-2 to ≥ 5 for each treatment group.[10] SIQ-Jr scores are reported as percent of patients with scores ≥ 31 for the total study population [3] and each treatment group,[13] percent of patients with score increase to ≥ 31,[10] and mean score for each treatment group.[3 10]

By week 36, CDRS-R scores are not described in any of the publications. For SIQ-Jr scores, results are described for patients who had completed the SIQ-Jr assessment at week 36 and for a smaller number of patients who both completed the assessment and were still in their assigned treatment group.[13] Results are presented as the percentage of patients with score ≥ 31 for each treatment group. Patients with score increases and mean scores are not reported.

Suicidal events are presented for all three treatment groups, and reported for intention-to-treat and observed cases groups. The frequency of suicidal events was calculated using the group size according to the original randomization, with no reference to the reduction in study group sizes.[13]

The publication by Vitiello et al [15] analyses suicidal events in more detail. Patients with high or increased scores, but not classified as having an event, were not included in the analysis. Nine cases of suicidal behaviour were presented as occurring in the PBO group, even though the patients were using fluoxetine at the time and the PBO period had ended. The paper reports on the number of cases, but does not include results from the suicidality scoring tools CDRS-R Item 13 and SIQ-Jr. The number of suicidal episodes was greater than it appears, as seven patients had more than one episode,[15] and only the most severe episode was included in the analysis.

The long term phase IV publication [16] present SIQ-Jr scores for a total of 66 patients who had at least one stage IV assessment. The paper refers to the baseline ITT groups of 327 patients (excluding PBO), but due to withdrawals any changes in scores may be biased, and reflect a selected study population rather than a treatment effect.

Reporting of psychiatric adverse effects/mania across TADS publications

The TADS study group found higher rates for psychiatric adverse events in patients receiving fluoxetine than in patients receiving CBT or PBO.[3 10] The psychiatric adverse events included symptoms classified as mania spectrum, irritability/depression spectrum, agitation spectrum, anxiety, or other. Of these, mania spectrum symptoms were described in greater detail in the 2006 safety publication.[10] We have therefore assessed and summarized the reporting of mania spectrum symptoms across the TADS publications (table 2).

Table 2 Reporting of mania symptoms in publications from the TADS study

Reporting parameter	Stage 1 (12 weeks)				Stage 2+3 (36 weeks)			Stage 4 (88 weeks)
	TADS 2004[3]	Emslie[10]	Kennard[11]	May[12]	TADS 2007[13]	Kennard[14]	Vitiello[15]	TADS 2009[16]
ADS Mania subscale score		Baseline: All 2,4 ± 2,3 COMB 2,6 ± 2,4 FLX 2,2 ± 2,2 CBT 2,5 ± 2,4 PBO 2,2 ± 2,3 12 weeks: All 0,9 ± 1,4 COMB 0,5 ± 0,8 FLX 1,1 ± 1,0 CBT 1,0 ± 1,2 PBO 1,1 ± 0,1					Baseline: 2,5 ± 2,2 Prior suicidal event: 1,6 ± 2,2 Mean change -0,6 ± 2,3	
ADS Mania subscale score increase (≥ 3 points)		All: 65/424 (15,3%) COMB 20% (n=21) FLX 14,2% (n=15) CBT 12,3% (n=13) PBO 15,0% (n=16)						
Patients with attrition prevent. mania/hypoman.				1,28% (calc.1/78)				
Mania	COMB 0 FLX 1 CBT 0 PBO 1	FLX 1						
Hypomania	COMB 1 FLX 2 CBT 0 PBO 1	COMB 1 FLX 2 PBO 1						
Elevated mood	COMB 0 FLX 1 CBT 0 PBO 0	FLX 1						

Mania spectrum symptoms (mania, hypomania and elevated mood) were monitored using an affective disorders screening procedure (ADS), as well as adverse event or serious adverse event forms. Due to the adverse event definition threshold, new cases of emerging mania were not recorded unless the symptoms caused clinically significant interference with functioning.[4]

Mania spectrum symptoms were mentioned in three of the four publications that reported on adverse effects in TADS during 0-12 weeks of treatment (stage I). The initial 2004 publication by the TADS study group reported a total of seven patients with mania spectrum symptoms as an adverse effect; four in the fluoxetine group, one in the COMB group, none in the CBT group, and two in the PBO group.[3] In the 2006 safety results publication,[10] occurrence of mania spectrum symptoms were reported based on both spontaneous reports and assessment by physician using a formal symptom checklist (ADS mania items). According to this publication, six patients spontaneously reported a mania spectrum disorder; four in the fluoxetine group, one in the COMB group, and one in the PBO group. On the ADS mania scoring scale, however, 65 of 424 patients across all treatment groups reportedly had an increase of 3 points or more. The absolute score increase for each patient or treatment group is not provided. The analysis of patients with at least one suicidal event (n=44) describes mean ADS mania score prior to the suicidal event for 31 of the 44 patients during 36 weeks of treatment.[15]

We did not identify any publication describing mania spectrum symptoms in the entire study population that received treatment for more than 12 weeks (stages II-IV) (table 2).

The publications from stage II-IV failed to mention psychiatric adverse effects that were identified during stage I, such as restlessness, nervousness and sleep difficulties (table 1).

Other adverse effects

Adverse effects other than suicidality were summed up by the TADS team in 2004,[3] reported in further detail in 2006 [10] and mentioned in the two other publications from study stage I to a varying extent.[11 12 17]According to the most extensive publication with regard to safety data at 12 weeks,[10] sedation, insomnia, vomiting and upper abdominal pain occurred at least twice as often in patients receiving fluoxetine with or without CBT than with PBO. We did not identify any publication describing non-psychiatric adverse effects in the study population that received treatment for more than 12 weeks (stages II, III, and IV) (table 1).

Adverse effects of fluoxetine, as acknowledged at present, are listed in table 3. The adverse effects are classified according to whether they were reported in any of the eight TADS publications or not. Several well known adverse effects of fluoxetine were not reported in the TADS publications, among them weight and appetite changes and effects on sexual functioning.

Table 3 TADS reporting of presently acknowledged common adverse effects of fluoxetine[18]

Mentioned in publications from the TADS study*	Not mentioned in publications from the TADS study
Insomnia	Decreased appetite, incl. anorexia
Sleep disorder	Weight decreased
Abnormal dreams, incl. nightmares	Tension
Anxiety	Libido decreased, incl. loss of libido
Somnolence, incl. hypersomnia, sedation	Gynaecological bleeding, incl. menstr.bleeding disorders
Nervousness	Erectile dysfunction
Restlessness	Ejaculation disorder
Headache	Dizziness
Disturbance in attention	Dysgeusia
Tremor	Lethargy
Palpitations	Vision blurred
Diarrhoea	Electrocardiogram QT prolonged
Nausea	Flushing, incl. hot flushes
Vomiting	Yawning
Dry mouth	Dyspepsia
Rash	Chills
Urticaria (hives)	Feeling jittery
Pruritus	
Hyperhidrosis	
Arthralgia	
Frequent urination	
Fatigue	

* Not necessarily identified as an adverse effect of fluoxetine treatment

Discussion

The TADS study protocol included a threshold limit on what would be considered an adverse event, specifying that the event must cause clinically significant interference with functioning, require medical attention, or cause a need to take medication.[3] As an example, emerging mania was not recorded unless symptoms exceeded this threshold.[4] It must be assumed that this reduced the number of reported adverse effects, which may not be severe enough to reduce daily functioning or cause a need for additional treatment. The protocol does not define how the scoring parameters for adverse events should be analyzed. The number of suicidal events are described, but other parameters, such as absolute or worsening scores on risk assessment scales, are not consistently reported. An example is the SIQ-Jr scores, where week 12 publications report mean scores and number of patients with score increase to ≥ 31,[3 10] while the follow-up publication by week 36 reports percent of patients with SIQ-Jr score ≥ 31.[13] Scoring of mania symptoms is described as inconsistent and varying between clinicians.[10] It is conceivable that some patients may have had worsening scores without passing the threshold score for suicidality or mania, respectively. Conversion into dichotomous scales, as was done for SIQ-Jr scores ≥ 31 and ADS Mania subscale score change increase ≥ 3 points, does not give insight into the magnitude in case of increased scores.

All analyses were planned as intention-to-treat (ITT), regardless of later events.[4] Nine cases of suicidal behaviour were presented as occurring in the PBO group [15] although the patients were using fluoxetine at the time and the PBO period had ended. As pointed out by Högberg et al. ,[8] the risk of suicidal behaviour will not appear to be increased for FLX compared to PBO if patients using FLX are assessed in the placebo group. ITT analyses of adverse events may be biased towards finding no differences between groups. [19] This is especially relevant in studies with large drop-out rates and in study groups where patients received a treatment that differed from the assigned medication, as was the case in the TADS study.[17] Other authors have

questioned whether the TADS study may have under-reported adverse effects due to small numbers and patients leaving the study early.[9] Use of ITT analyses will have led to artificial lowering of the frequency estimates for psychiatric and other adverse events, a fact which has been little discussed.

Risk of suicidal behaviour was the only adverse effect that was addressed during all four treatment stages. Several psychiatric- and physical adverse effects were reported during the first 12 weeks, but not mentioned in publications from the further treatment stages. Examples are sedation, insomnia, vomiting, and upper abdominal pain, which occurred in more than 2% of patients in the first 12 weeks.[10] The 2% occurrence is described as infrequent (≤ 5%), but should more correctly be classified as common.[20] Other adverse effects of SSRI treatment, such as appetite changes, weight changes and sexual problems, are not mentioned in any publication. Growth issues were not addressed. Changes in weight or appetite may have occurred without reaching the severity threshold. Sexual adverse effects may not be forthcoming in interviews, especially as many patients were interviewed in the company of caregivers [10] and may not have been relevant to many patients at the time due to their age. Prolonged treatment into adulthood may well increase the relevance of such concerns.

To our knowledge, this is the first systematic assessment of adverse effects reporting in publications from the TADS study. We conducted an extensive literature search and believe that all relevant studies have been identified, however we can not exclude the possibility that some publications may have been overlooked.

A previous assessment of the adverse effects reporting in TADS focused on the occurrence of suicidal events and increased risk of suicidal behaviour.[8] Like Högberg et al,[8] we have noted the misleading PBO group classification of patients with a suicidal event who were using FLX at the time. Our analysis encompasses all adverse events mentioned in publications from the TADS study. Gaps and discrepancies in coding, transcription and reporting of harms in clinical trials have been reported, and the number of adverse events may differ between study reports and published papers [21 22]. Several barriers to accurate harms reporting [21] are relevant to the TADS study, notably the severity threshold, conversions from continuous to dichotomous outcomes, individual judgments of association between event and medication, handling of adverse events in patients who discontinued treatment, and the extensive use of concomitant medications.

Due to its long duration (36 weeks) and follow-up (1 year), the TADS study could have provided valuable information on the long-term occurrence of adverse effects both in frequency and severity. The adverse effects profile of FLX in the TADS has only been reported in detail for stage 1, where approximately 200 patients received FLX for 12 weeks. The raw data from the trial have been requested [23] and planned for release into the public domain,[24] but we have not been able to ascertain that these have been made available. The incomplete reporting of adverse effects in a major study may lead to bias and erroneous conclusions regarding the safety profile of fluoxetine given to minors.

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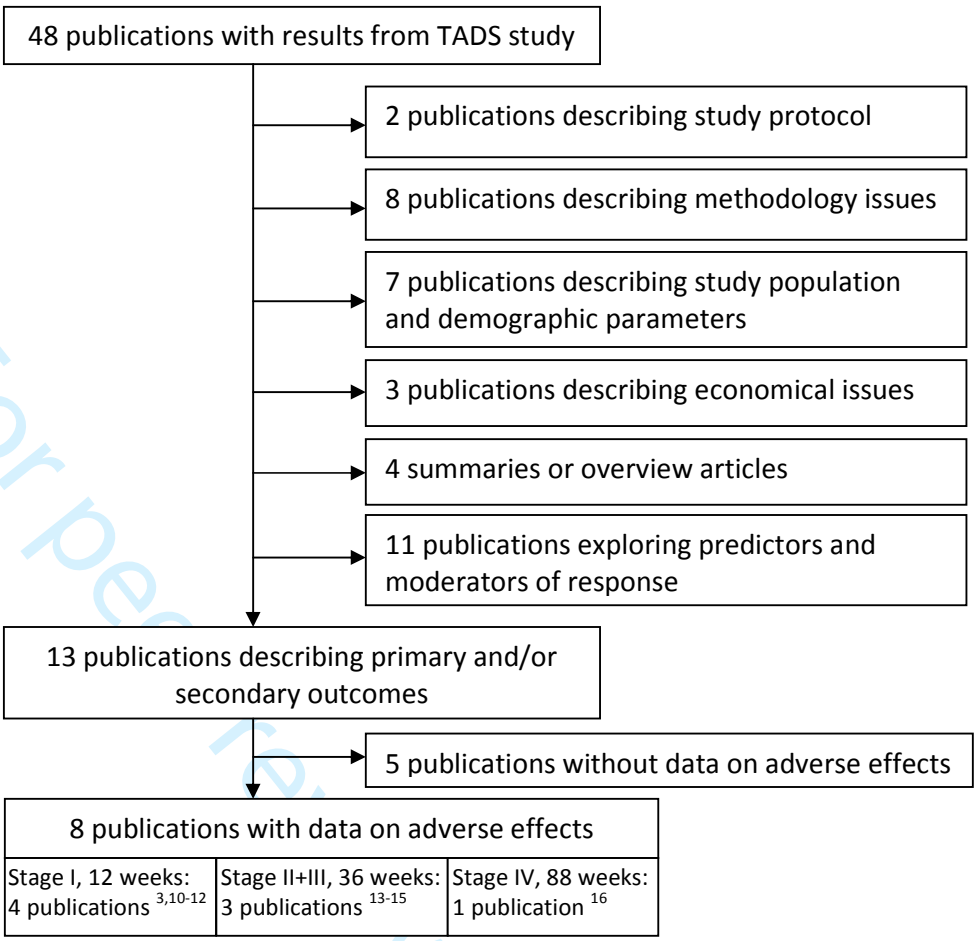
Contributors: SN suggested the research question. All authors discussed and defined the project. TW and SN researched the literature and made the initial assessments. All authors discussed the publications included in the study, including interpretation and presentation of results. TW drafted and finalized the manuscript as lead author. SN and MK commented on the draft and revised the manuscript at all stages.

Figure 1 Selection and characteristics for publications from the TADS study



Supplementary file. Reporting of suicidality in publications from the TADS study

		Stage 1 (12 weeks)				Stage 2+3 (36 weeks)			Stage 4 (88 weeks)
Reporting parameter		TADS 2004[3]	Emslie[10]	Kennard[11]	May[12]	TADS 2007[13]	Kennard[14]	Vitiello[15]	TADS 2009[16]
CDRS-R Item 13	% patients CDRS-R Item 13 score ≥2	Baseline: 27% 12 wk: 9.4%							
	% patients CDRS-R Item 13 score ≥6	Baseline: 2%							
	% patients CDRS-R Item 13 score ≥3		Baseline: 21.4%						
	% patients worsening CDRS-R Item 13 ≥1 point		COMB 5% FLX 13.4% CBT 15.2% PBO 7.2%						
	% patients increase CDRS Item 13 from 1-2 to ≥ 5		COMB 0 FLX 3.7% CBT 1.3% PBO 2.6%						
SIQ-Jr	% patients SIQ-Jr score ≥ 31	Baseline: 29% 12 wk: 10.3%	Baseline: 29.2%			Baseline: 97/320 (30.3%) FLX 28/107 (26.2%) COMB 42/106 (39.6%) CBT 27/107 (25.2%) **Stage 1 (12 wk)** **Completed score** **Observed cases** All: 31/278 (11.2%) All: 24/257 (9.3%) COMB 8/90 (8.9%) COMB 5/84 (6.0%) FLX 18/97 (18.6%) FLX 14/89 (15.7%) CBT 5/91 (5.5%) CBT 5/84 (6.0%) **Stage 3 (36 wk)** All: 15/228 (6.6%) All: 10/171 (5.8%) COMB 2/79 (2.5%) COMB 0/63 (0%) FLX 10/73 (13.5%) FLX 8/55 (14.5%) CBT 3/76 (3.9%) CBT 2/53 (3.8%)			Baseline: COMB 1/78 (1.3%) FLX 4/73 (5.5%) CBT 0/76 (0%)
	% patients SIQ-Jr score increase to ≥ 31		All: 4.8% (18/374) COMB 2.2% (2/93) FLX 7.3% (7/96) CBT 2.2% (2/93) PBO 7.6% (7/92)						All: 6.4% COMB 5.9% FLX 7.6% CBT 6.4%
	SIQ-Jr score adjusted mean ±SD	Baseline: COMB 27.33 (18.51) FLX 21.81 (14.44) CBT 21.91 (16.28) PBO 24.20 (16.46) 12 wk: COMB 11.79 (11.69) FLX 14.44 (11.13) CBT 11.40 (10.44) PBO 15.01 (11.05)	12 wk: COMB 10.9 ± 0.3 FLX 13.7 ±0.2 CBT 11.3 ±0.3 PBO 14.5 ± 0.6						36 wk: COMB 10.2 ± 8.8 FLX 12.1 ± 11.1 CBT 9.5 ± 9.1 88 wk: COMB 9.3 ± 7.8 FLX 10.5 ± 10.4 CBT 8.2 ± 8.1

Supplementary file. Reporting of suicidality in publications from the TADS study, cont'd.

Number of cases	Harm-related AE†	All: 33/439 (7.5%) Serious: 23/33 (69.7%) COMB 9/107 (8.41%) FLX 13/109 (11.93%) CBT 5/111 (4.50%) PBO 6/112 (5.36%)							
	Suicide-related AE†	All: 24/439 (5.5%) COMB 6/107 (5.61%) FLX 9/109 (8.26%) CBT 5/111 (4.50%) PBO 4/112 (3.57%)	24 (5.5%) COMB 5 (4.7) FLX 10 (9.2%) CBT 5 (4.5%) PBO 3 (2.7%)		16/78				
	Suicidal event†					**Stage 1 (12 wk)** **Observed cases** / **Intention-to-treat** All: 20/327 (6.1%) / All: 22/327 (6.7%) COMB 5/107 (4.7%) / COMB 5/107 (4.7%) FLX 10/109 (9.2%) / FLX 12/109 (11.0%) CBT 5/111 (4.5%) / CBT 5/111 (4.5%) **Stage 3 (36 weeks)** All: 26/327 (8.0%) / All: 32/327 (9.8%) COMB 8/107 (7.5%) / COMB 9/107 (8.4%) FLX 12/109 (11.0%) / FLX 16/109 (14.7%) CBT 6/111 (5.4%) / CBT 7/111 (6.3%)	**Stage 2-3 (12-36 wk)** PBO/Open 10.7% (12/112) Active 32/327 (9.8%)	All: 44/439 (10.0%) COMB 9/107 (8.4%) FLX 16/109 (14.7%) CBT 7/111 (6.3%) (5 CBT, 2 FLX at event) PBO 12/112 (10.7%) (3 PBO, 9 FLX at event) SSRI at event: 36	
	Suicidal. inc. self-harm				27/78 (37.6%)				
	Thoughts self-harm				8/27 (29.6%)				
	Plan self-harm				8/27 (29.6%)				
	Intent self-harm				4/27 (14.8%)				
	Attempt self-harm				All: 7/27 (25.9%) COMB 1 FLX 4 CBT 1 PBO 1				
	Intend, plan, attempt self-harm				All: 16 COMB 3 FLX 7 CBT 3 PBO 4				
	Intend, plan, attempt suicide (Columbia reassess.)				All: 9 COMB 2 FLX 3 CBT 2 PBO 2				
	Suicidal ideation†		All: 18 (4.1%) COMB 3 (2.8%) FLX 8 (7.3%) CBT 4 (3.6 %)	6/129 (remitters, from fig.)				All 23/439 (5.2%)	

			PBO 3 (2.7%)						
	Suicide-related AE, Columbia 1,2,6 †		All: 23 (5.2%) COMB 5 (4.7%) FLX 10 (9.2%) CBT 5 (4.5%) PBO 3 (2.7%)						
	Suicide-related AE, Columbia 1,2,3,6 †		All: 24 (5.5%) Serious: 15 COMB 6 (5.6%) FLX 10 (9.2%) CBT 5 (4.5%) PBO 3 (2.7%)						
	Attempt suicide†	All: 7/439 (1.6%) COMB 4 FLX 2 CBT 1	All: 5 COMB 2 FLX 2 CBT 1 PBO 0					All 21/439 (4.8%)	

† Frequency calculations based on ITT groups

ENTREQ Checklist

Critical appraisal of adverse effects reporting in the "Treatment for Adolescents With Depression Study (TADS)" study. Westergren et al.

No	Item	Guide and description
1	Aim	Background:The "Treatment for Adolescents With Depression Study (TADS)" study was performed in 2000-2003. The study included 439 youths who were randomized to treatment with fluoxetine, cognitive behavioral therapy, cognitive behavioral therapy plus fluoxetine, or placebo. The study is regarded as a high-quality study and is referred to in most systematic reviews and treatment recommendations on the effectiveness and risk of antidepressant therapy in adolescents. Objective: To identify all publications from the TADS study and assess the publications with regard to reporting of adverse effects in the treatment groups both for the short-term and long-term study stages.
2	Synthesis methodology	Descriptive (whether adverse effects were presented and which adverse effects were presented)
3	Approach to searching	Pre-planned search, with a comprehensive search strategy
4	Inclusion criteria	All available studies arising from the TADS study, assessed for mention of adverse effets
5	Data sources	Searches in PubMed, EMBASE, Psychinfo, Google Scholar search and clinicaltrials.gov, by hand searching of references in identified publications, and by searching other publications by the main authors. Searches conducted June 2017-February 2018. Rationale for using the data sources: Known publications found in PubMed and EMBASE. One treatment arm was for cognitive therapy, and it was possible that there publications could be found in PsychInfo.

No	Item	Guide and description
6	Electronic Search strategy	Search terms in Google Scholar were either «TADS team» or «Treatment for adolescents with depression study». Search term in PsycINFO was «Treatment for adolescents with depression study». Search term in PubMed was the phrase «Treatment for adolescents with depression study» and similar publications, limited from 2004 to September 2017 and age group Child 0-18. Search term in Embase was «Treatment for adolescents with depression study».
7	Study screening methods	Authors TW and SN reviewed study abstracts to identify publications from the TADS study. All identified studies were reviewed in full text to assess whether they reported adverse effects.
8	Study characteristics	All included publications refer to the same study: The "Treatment for Adolescents With Depression Study (TADS)" study. Included studies refer to different study stages or study populations and were published from 2004-2009.
9	Study selection results	We screened 48 TADS publications and excluded 40 for not providing any information on adverse effects. The selection process in described in Figure 1.
10	Rationale for appraisal	We intended to identify any TADS publication that gave some information on adverse effects, without further quality assessment or limitations, in order to include all possibly relevant data.
11	Appraisal items	See over
12	Appraisal process	Appraisal was conducted independently by two reviewers. Appraisal was discussed bya third reviewer in case of doubt or disagreement.

No	Item	Guide and description
13	Appraisal results	No articles identified as giving information on adverse effects were excluded for quality or other reasons.
14	Data extraction	All adverse effects mentioned in text or tables were extracted and included in overview tables.
15	Software	No analysis computer software
16	Number of reviewers	Tone Westergren, Sigrid Narum, Marianne Klemp.
17	Coding	No coding
18	Study comparison	Adverse effects reported or referred to as described in original studies, without recoding
19	Derivation of themes	Not relevant; Descriptive process
20	Quotations	Not relevant
21	Synthesis output	Our findings raise the question of whether this central study, and the large number of publications arising from it, has generated a perception that adverse effects of fluoxetine were well documented both in short-term and long-term treatment. In fact, the risk/benefit assessments during the later study stages narrowed the risk factors down to one factor only; the risk of suicidal events. Other, more common, adverse effects are not part of the total risk assessment in short- or long-term use, thereby skewing the perceived risk/benefit relationship.

BMJ Open

Critical appraisal of adverse effects reporting in the "Treatment for Adolescents With Depression Study (TADS)" study

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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Evidence based practice, Mental health, Paediatrics
Keywords:	CLINICAL PHARMACOLOGY, Child & adolescent psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS

Critical appraisal of adverse effects reporting in the "Treatment for Adolescents With Depression Study (TADS)" study

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Competing interest statement
All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Patient consent: Not relevant

Data sharing: No additional data available

ABSTRACT

Objective To identify all publications from the "Treatment for Adolescents With Depression Study (TADS)" study and assess the findings regarding occurrence of any adverse effects in the treatment groups both for the short-term and long-term study stages.

Design Descriptive analysis of TADS study publications with any information on adverse effects.

Results We identified 48 publications describing various aspects of the TADS study, in which 439 adolescent patients received treatment with fluoxetine, cognitive behavioural therapy (CBT), cognitive behavioural therapy plus fluoxetine, or placebo. Eight publications were assessed as providing some data on adverse effects. Risk of suicidal behaviour was the only adverse effect that was addressed in all publications. Several psychiatric and physical adverse effects were reported during the first 12 weeks, but not mentioned in reports from later study stages. Common adverse effects of fluoxetine, such as weight changes or sexual problems, were not identified or mentioned in the publications.

Conclusions The TADS study publications do not present a comprehensive assessment of treatment risk with fluoxetine in adolescents, especially for more than 12 weeks of treatment. Risk of suicidality was the only adverse effect that was reported over time. Reporting of adverse effects was incomplete with regard to the long-term safety profile of fluoxetine.

Strengths and limitations of this study

- This is the first systematic assessment of adverse effects reporting in publications from the TADS study.
- The analysis encompasses all adverse events mentioned in publications from the TADS study.
- An extensive literature search was conducted and we believe that all relevant studies have been identified
- We cannot exclude the possibility that some publications may have been overlooked.

Critical appraisal of adverse effects reporting in the "Treatment for Adolescents With Depression Study (TADS)" study

INTRODUCTION

The safety profile of SSRIs in adolescents has been extensively debated. Several systematic reviews have analysed what is known about the risk of suicidal behaviour [1-3] as well as other psychiatric and somatic adverse risks and the perceived benefit/risk balance. The reviews have highlighted considerable variations in assessment, definitions and reporting of adverse effects in the clinical trials.

The Norwegian Regional Medicines Information & Pharmacovigilance Centres (RELIS) and the Centre for Psychopharmacology at Diakonhjemmet Hospital regularly receive queries from hospital doctors and general practitioners regarding the safety of fluoxetine and other selective serotonin reuptake inhibitors in adolescent patients.

One of the major clinical studies of efficacy and safety of fluoxetine in adolescents is the "Treatment for Adolescents With Depression Study (TADS)", which is often referred to in textbooks and reviews.

In 1998, the US National Institute of Mental Health (NIMH) issued a request for proposals (RFP-NIH-NIMH 98-DS-0008) with the objective of launching a clinical trial to address the effectiveness of treatment for adolescents with major depression.[4] The subsequent study, "Treatment for Adolescents With Depression Study (TADS)" was coordinated by the Department of Psychiatry and Behavioral Sciences and the Duke Clinical Research Institute, both at Duke University Medical Center, collaborating with and funded by NIMH,[5] and carried out in the period 2000-2003.[6] The study included 439 youths who were randomized to one of four treatment groups; 1) fluoxetine (FLX), 2) cognitive behavioural therapy (CBT), 3) cognitive behavioural therapy plus fluoxetine (COMB), or 4) placebo (PBO) for twelve weeks (stage I).[6] Double blind treatment was performed among patients treated with fluoxetine and placebo only, while patients treated with CBT with or without fluoxetine received open treatment. Stage II and III were maintenance phases for the active treatment groups, with the option of intensifying treatment for partial responders. Patients in the placebo group were offered open active treatment of fluoxetine, CBT or both. Stage IV consisted of an additional year of open follow-up.[5]

The two primary outcome measures in the TADS study were Children's Depression Rating Scale-Revised (CDRS-R) total scores, and responder status on the Clinical Global Impressions-Improvement (CGI-I) scale. According to protocol, all analyses would be performed by intention to treat (ITT), regardless of later events.

Adverse events during the acute and maintenance phases were defined as secondary outcomes.[7] Patients were monitored for safety regarding affective disorders, need for mental health treatment, need for concomitant medications, occurrence of adverse events and serious adverse events, and use of adjunctive services and attrition prevention (ASAP). Most assessments were based on both patient and parent information.[8]

The TADS study has been described as the largest and arguably the highest-quality acute-phase randomized placebo controlled trial of an antidepressant drug for adolescent depression.[9] We understand from the protocol and monitoring procedures that the TADS study team intended to evaluate the tolerability of treatment, and that the study was expected to provide improved

insight into the potential adverse effects of antidepressant treatment in this age group, due to its study size and duration. Several publications from the TADS study have addressed risks of adverse effects. Despite this, concerns have been raised regarding underreporting of suicidal risk,[10] study size and an increased risk of psychiatric adverse effects.[11]

In the TADS study, adverse events were defined as an unfavourable medical change that occurred after beginning or during the study that might or might not be related to or caused by the study drug or CBT treatment. This was further specified as any medical event that caused clinically significant interference with functioning (e.g. headache that caused school absence or otherwise causes clinically significant activity restriction), any event that required medical attention, and any medical event associated with impairment in functioning and induced the patient to take a concomitant medication. Conditions that did not lead to clinically significant interference with functioning or did not require medical attention were not defined as adverse events.[7, 8] The protocol specified that new onset psychiatric symptoms such as emerging mania or panic attacks would be recorded if they caused clinically significant interference with functioning.[8] It follows that such conditions would not be recorded unless a certain severity threshold was reached.

Harm-related adverse events were defined as involving harm to self, which could include a non-suicidal event. Examples given are cutting, worsening of suicidal ideation, suicide attempt or harm to others. Suicide-related adverse events were defined as worsening suicidal ideation and/or suicide attempt. Adverse Event Forms were to be used throughout the study and it must be assumed that such data were collected, as well as clinical scoring data for possible psychiatric adverse events.

Our objective in the present study was to identify all publications from the TADS study and assess the findings regarding occurrence of any adverse effects in the treatment groups both for the short-term and long-term study stages. The TADS study was chosen because of the non-industrial funding and because it is considered as a high-quality study.[9]

METHODS

Literature search

Publications from the TADS study were identified through searches in PubMed, EMBASE, Psychinfo, Google Scholar, clinicaltrials.gov, National Institute of Mental Health website nimh.nih.gov, the Duke Clinical Research Institute TADS website (http://tads.dcri.org), by hand searching of references in identified publications, and by searching other publications by the main authors (snowballing). Search terms in Google Scholar were either «TADS team» or «Treatment for adolescents with depression study». Search term in PsycINFO was «Treatment for adolescents with depression study». Search term in PubMed was the phrase Treatment for adolescents with depression study. The initial publications with data from the TADS study were identified and used to search for similar publications, limited to 2004 to 1. September 2017, Clinical Trial or Randomized Controlled Trial and age group Child 0-18. Search term in Embase was «Treatment for adolescents with depression study». The final main search in all databases was conducted on September 5th, 2017. An additional literature search in PubMed for any recent TADS publications was conducted in February 2018 and updated in January 2019.

Inclusion and exclusion criteria

Identified TADS publications were assessed and classified according to publication topic and reported outcomes. Inclusion criteria: All publications that reported on results from the TADS study and provided some information on adverse effects. Publications on efficacy or non-

primary or non-secondary outcomes were excluded if they gave no information on adverse events.

Data assessment

Adverse effects were defined as psychiatric or somatic diagnoses or complaints arising during treatment, as described in the publications. In addition, we have included worsening of depression as an adverse effect if described in the publications. Publications describing any adverse events during treatment were analysed in detail regarding the types and frequency estimates of adverse events. Two researchers (TW and SN) evaluated each publication independently. All researchers (TW, SN and MK) discussed any ambiguity and the data extraction tables.

Patient and Public Involvement

Patients or the public were not involved in this literature review.

RESULTS

We identified 48 publications that reported on the study protocol and/or various outcomes in the TAD study population. The selection process and publication characteristics are described in figure 1.

Eight publications were assessed as providing at least some data on adverse effects, [6, 12-18] of which four publications reported possible adverse effects for subgroups of patients only; patients who responded to treatment,[13] patients originally assigned to placebo treatment,[16] patients who had at least one suicidal event,[17] and patients using attrition prevention services,[14] respectively. Reporting of adverse effects was most detailed in the two initial results publications from stage I (0-12 weeks),[6, 12] and included a wide range of adverse effects, including several psychiatric and gastrointestinal reactions. One stage I publication did not address adverse effects explicitly; however, symptoms that may be associated with adverse effects were described as residual symptoms of depression.[13]

The publications that reported on adverse effects in the later study stages II, III, and IV listed few adverse effects except suicidal behaviour (table 1). The publication that purported to report on long-term effectiveness and safety outcomes only included reporting of suicide-related adverse events.[15]

Table 1 Reporting of adverse events in publications from the TADS study

Reported event	Stage 1 (12 wk)				Stage 2+3 (36 wk)			Stage 4 (88 wk)
	TADS[6]	Emslie[12]	Kennard[13]$^{\alpha}$	May[14]$^{\beta}$	TADS[15]	Kennard[16]$^{\gamma}$	Vitiello[17]$^{\delta}$	TADS[18]
Harm-related adverse event	x	x		x				
Suicide-related adverse event	x	x	x *	x	x	x	x	x
Attempted suicide	x	x		x	x	x	x	
Homicidality		x		x				
Mania	x	x		x			x	
Hypomania	x	x		x				
Elevated mood	x	x						
Trouble attention/concentration		x	x *					
Racing thoughts		x						
Excessive talking/talking very		x						
Increase in activities		x						
Impulsivity		x						
Hypersensitivity **	x	x						
Irritability	x	x	x *				x	
Anger	x	x						
Worsening of depression	x	x		x		x	x	x
Psychomotor			x *					
Guilt			x *					
Mood			x *					
Interest			x *					
Crying	x	x						
Agitation	x	x						
Akathisia	x	x						
Nervousness	x	x						
Restlessness	x	x						
Hyperactivity	x	x						
Panic attacks	x	x						
Anxiety	x	x						
Excessive sweating		x						
Difficulty breathing		x						
Hearing problems		x						
Somnolence/feeling drowsy	x	x						
Insomnia/sleeplessness	x	x					x	
Sleep	x	x	x *					
Nightmare	x	x						
Night sweats	x							
Sedation	x	x						
Fatigue	x		x *					
Tremor	x	x						
Behaviour/feeling abnormal	x	x						
Social problems				x			x	
Headache	x	x						
Upper abdominal pain	x	x						
Stomach pain		x						
Diarrhea	x	x						
Influenza/sinusitis	x							
Cold, sore throat, cough/wheez		x						
Allergies		x						
Dry mouth		x						
Nausea/vomiting	x	x						
Fever		x						
Muscle aches or cramps		x						
Joint pain		x						
Numbness or tingling arms or legs		x						
Weight			x *					
Chest pain		x						
Racing/pounding heart, skip		x						
Urination frequency or pain		x						
Constipation, feeling bloated		x						
Skin rash/hives		x						

α Reporting limited to responders subgroup, regardless of treatment arm
β Reporting limited to subgroup of patients seeking attrition prevention
γ Reporting limited to ITT placebo group
δ Reporting limited to patients with a suicidal event
* Reported as residual symptoms of depression
** Understood as mood hypersensitivity

Patient population and treatment modifications during the study

In the TADS study, 439 patients were randomized to one of the four treatment groups. By the end of stage I (12 weeks), 351 patients remained for assessment, of them 270 patients in active treatment groups. The rest of the patients had either withdrawn their consent, or been classified as premature terminators due to need for additional treatment.[6,15] It is not specified to what extent dropouts or premature terminations were due to adverse events in the initial study population and if those adverse events were included in the reports. By week 36 (end of stage III), 178 patients remained in the group to which they had been randomized, specifically 68 for COMB, 55 for FLX and 55 for CBT.[15] Patients who terminated their assigned treatment prematurely did in many cases continue their assessments and were included in the ITT analyses for their original group, although they received an active treatment other than that specified for the group they were assigned to.[12, 15, 19] Between 34 and 46% of patients in the monotherapy groups did not remain in their assigned treatment arm by the end of stage II, and 43 of the 111 patients (38%) in the CBT group were receiving another SSRI or antidepressant by the end of stage III (36 weeks).[19]

Reporting of suicidality in TADS publications

Suicidality symptoms were monitored using an affective disorders screening procedure (ADS), Reynolds adolescent depression scale (RADS), a revised Children's Depression Rating Scale (CDRS-R), a Suicide Ideation Questionnaire (SIQ-Jr) as well as adverse event/serious adverse event forms. All the TADS publications classified as reporting adverse effects [6, 12-18] describe the risk of suicidal events, defined as discrete episodes of suicidal ideation, suicidal attempts, or preparatory acts toward an imminent attempt. Injury to self was not included if there was no suicidal intent. Reporting of suicidal events and -risk is described in the supplementary file. Data on suicidality are presented as either counts of discrete episodes, mean scores, score changes or proportion of patients reaching threshold values on scoring tools.

By week 12, CDRS-R item 13 scores are reported as percent of patients with score ≥ 2 for the total study population,[6] percent of patients with score worsening ≥ 1 point, and percent of patients with score increase from 1-2 to ≥ 5 for each treatment group.[12] SIQ-Jr scores are reported as percent of patients with scores ≥ 31 for the total study population [6] and each treatment group,[15] percent of patients with score increase to ≥ 31,[12] and mean score for each treatment group.[6, 12]

By week 36, CDRS-R scores are not described in any of the publications. For SIQ-Jr scores, results are described for patients who had completed the SIQ-Jr assessment at week 36 and for a smaller number of patients who both completed the assessment and were still in their assigned treatment group.[15] Results are presented as the percentage of patients with score ≥ 31 for each treatment group. Patients with score increases and mean scores are not reported.

Suicidal events are presented for all three treatment groups, and reported for intention-to-treat and observed cases groups. The frequency of suicidal events was calculated using the group size according to the original randomization, with no reference to the reduction in study group sizes.[15]

The publication by Vitiello et al [17] analyses suicidal events in more detail. Patients with high or increased scores, but not classified as having an event, were not included in the analysis. Nine cases of suicidal behaviour were presented as occurring in the placebo group, even though the patients were using fluoxetine at the time and the placebo period had ended. The paper reports on the number of cases, but does not include results from the suicidality scoring tools CDRS-R Item 13 and SIQ-Jr. The number of suicidal episodes was greater than it appears, as

seven patients had more than one episode,[17] and only the most severe episode was included in the analysis.

The long term phase IV publication [18] present SIQ-Jr scores for a total of 66 patients who had at least one stage IV assessment. The paper refers to the baseline ITT groups of 327 patients (excluding placebo), but due to withdrawals any changes in scores may be biased, and reflect a selected study population rather than a treatment effect.

Reporting of psychiatric adverse effects/mania across TADS publications

The TADS study group found higher rates for psychiatric adverse events in patients receiving fluoxetine than in patients receiving CBT or placebo.[6, 12] The psychiatric adverse events included symptoms classified as mania spectrum, irritability/depression spectrum, agitation spectrum, anxiety, or other. Of these, mania spectrum symptoms were described in greater detail in the 2006 safety publication.[12] We have therefore assessed and summarized the reporting of mania spectrum symptoms across the TADS publications (table 2).

Table 2 Reporting of mania symptoms in publications from the TADS study

Reporting parameter	Stage 1 (12 wk)				Stage 2+3 (36 wk)			Stage 4 (88 wk)
	TADS[6]	Emslie[12]	Kennard [13]	May [14]	TADS[15]	Kennard [16]	Vitiello[17]	TADS[18]
ADS Mania subscale score		**Baseline:** All: 2,4 ± 2,3 COMB: 2,6 ± 2,4 FLX: 2,2 ± 2,2 CBT: 2,5 ± 2,4 PBO: 2,2 ± 2,3 **12 weeks:** All: 0,9 ± 1,4 COMB: 0,5 ± 0,8 FLX: 1,1 ± 1,0 CBT: 1,0 ± 1,2 PBO: 1,1 ± 0,1					**Baseline:** 2,5 ± 2,2 **Prior to suicidal event:** 1,6 ± 2,2 **Mean change before event :** -0,6 ± 2,3	
ADS Mania subscale score increase (≥ 3 points)		All: 65/424 (15,3%) COMB: 20% (n=21) FLX: 14,2% (n=15) CBT: 12,3% (n=13) PBO: 15,0% (n=16)						
Patients with attrition prevention due tomania/hypomania				1,28% (1/78)				
Mania	COMB: n=0 FLX: n=1 CBT: n= 0 PBO: n= 1	FLX : n= 1						
Hypomania	COMB: n=1 FLX: n=2 CBT: n=0 PBO: n=1	COMB: n=1 FLX: n=2 PBO: n=1						
Elevated mood	COMB: n=0 FLX: n=1 CBT: n=0 PBO: n=0	FLX: n=1						

Mania spectrum symptoms (mania, hypomania and elevated mood) were monitored using an affective disorders screening procedure (ADS), as well as adverse event or serious adverse event forms. Due to the adverse event definition threshold, new cases of emerging mania were not recorded unless the symptoms caused clinically significant interference with functioning.[7]

Mania spectrum symptoms were mentioned in three of the four publications that reported on adverse effects in TADS during 0-12 weeks of treatment (stage I). The initial 2004 publication by the TADS study group reported a total of seven patients with mania spectrum symptoms as an adverse effect; four in the fluoxetine group, one in the COMB group, none in the CBT group, and two in the placebo group.[6] In the 2006 safety results publication,[12] occurrence of mania spectrum symptoms were reported based on both spontaneous reports and assessment by physician using a formal symptom checklist (ADS mania items). According to this publication, six patients spontaneously reported a mania spectrum disorder; four in the fluoxetine group, one in the COMB group, and one in the placebo group. On the ADS mania scoring scale, however, 65 of 424 patients across all treatment groups reportedly had an increase of 3 points or more. The absolute score increase for each patient or treatment group is not provided. The analysis of patients with at least one suicidal event (n=44) describes mean ADS mania score prior to the suicidal event for 31 of the 44 patients during 36 weeks of treatment.[17]

We did not identify any publication describing mania spectrum symptoms in the entire study population that received treatment for more than 12 weeks (stages II-IV) (table 2).

The publications from stage II-IV failed to mention psychiatric adverse effects that were identified during stage I, such as restlessness, nervousness and sleep difficulties (table 1).

Other adverse effects

Adverse effects other than suicidality were summed up by the TADS team in 2004,[6] reported in further detail in 2006 [12] and mentioned in the two other publications from study stage I to a varying extent.[13, 14, 19] According to the most extensive publication with regard to safety data at 12 weeks,[12] sedation, insomnia, vomiting and upper abdominal pain occurred at least twice as often in patients receiving fluoxetine with or without CBT than with placebo. We did not identify any publication describing non-psychiatric adverse effects in the study population that received treatment for more than 12 weeks (stages II, III, and IV) (table 1).

Adverse effects of fluoxetine, as acknowledged at present, are listed in table 3. The adverse effects are classified according to whether they were reported in any of the eight TADS publications or not. Several well-known adverse effects of fluoxetine were not reported in the TADS publications, among them weight and appetite changes. Effects on sexual functioning are not mentioned in this group of young patients.

Table 3 TADS reporting of presently acknowledged common adverse effects of fluoxetine[20]

Mentioned in publications from the TADS study*	Not mentioned in publications from the TADS study
Insomnia	Decreased appetite, incl. anorexia
Sleep disorder	Weight decreased
Abnormal dreams, incl. nightmares	Tension
Anxiety	Libido decreased, incl. loss of libido
Somnolence, incl. hypersomnia, sedation	Gynaecological bleeding, incl. menstrual bleeding disorders
Nervousness	Erectile dysfunction
Restlessness	Ejaculation disorder
Headache	Dizziness
Disturbance in attention	Dysgeusia
Tremor	Lethargy
Palpitations	Vision blurred
Diarrhoea	Electrocardiogram QT prolonged
Nausea	Flushing, incl. hot flushes
Vomiting	Yawning
Dry mouth	Dyspepsia
Rash	Chills
Urticaria (hives)	Feeling jittery
Pruritus	
Hyperhidrosis	
Arthralgia	
Frequent urination	
Fatigue	

* Not necessarily identified as an adverse effect of fluoxetine treatment

DISCUSSION

The TADS study protocol included a threshold limit on what would be considered an adverse event, specifying that the event must cause clinically significant interference with functioning, require medical attention, or cause a need to take medication.[6] As an example, emerging mania was not recorded unless symptoms exceeded this threshold.[7] It must be assumed that this reduced the number of reported adverse effects, which may not have been severe enough to reduce daily functioning or cause a need for additional treatment. We have not been able to find a published version of the questionnaires that were used and consequently do not have information as to which adverse effects were specifically asked for. The protocol does not define how the scoring parameters for adverse events should be analysed. The number of suicidal events are described, but other parameters, such as absolute or worsening scores on risk assessment scales, are not consistently reported. An example is the SIQ-Jr scores, where week 12 publications report mean scores and number of patients with score increase to ≥ 31,[6, 12] while the follow-up publication by week 36 reported percent of patients with SIQ-Jr score ≥ 31.[15] Scoring of mania symptoms are described as inconsistent and varying between clinicians.[12] It is conceivable that some patients may have had worsening scores without passing the threshold score for suicidality or mania, respectively. Conversion into dichotomous scales, as was done for SIQ-Jr scores ≥ 31 and ADS Mania subscale score change increase ≥ 3 points, does not give insight into the magnitude in case of increased scores.

All analyses were planned as intention-to-treat (ITT), regardless of later events.[7] Nine cases of suicidal behaviour were presented as occurring in the placebo group [17] although the patients were using fluoxetine at the time and the placebo period had ended. As pointed out by Högberg et al.,[10] the risk of suicidal behaviour will not appear to be increased for fluoxetine compared to placebo if patients using fluoxetine are assessed in the placebo group. ITT analyses of adverse events may be biased towards finding no differences between groups.[21] This is especially relevant in studies with large drop-out rates and in study groups where patients received add-on treatment that differed from the assigned medication, as was the case in the TADS study.[19] Other authors have questioned whether the TADS study may have

under-reported adverse effects due to small numbers and patients leaving the study early.[11] Use of ITT analyses will have led to underestimation of the frequency of psychiatric and other adverse events, a fact which has been little discussed.

Risk of suicidal behaviour was the only adverse effect that was addressed during all four treatment stages. Several psychiatric- and physical adverse effects were reported during the first 12 weeks, but not mentioned in publications from the further treatment stages. Examples are sedation, insomnia, vomiting, and upper abdominal pain, which occurred in more than 2% of patients in the first 12 weeks.[12] The 2% occurrence is described as infrequent (≤ 5%), but should more correctly be classified as common.[22] The risk of psychiatric adverse events such as mania, irritability, agitation and anxiety is given as 11% in the FLUOXETINE group and 5,6% in the COMB group [12]. In the review by Garland, the occurrence of emotional/behavioural adverse effects is given as 10-25% [3], but the numbers may not be comparable due to different inclusion criteria. Other adverse effects of SSRI treatment, such as appetite changes, weight changes and sexual problems, are not mentioned in any publication. Growth issues were not addressed. Changes in weight or appetite may have occurred without reaching the severity threshold. Sexual adverse effects may not have been relevant to many patients at the time due to their age, or may not have been forthcoming in interviews, especially as many patients were interviewed in the company of caregivers [12]. Risk of sexual adverse effects was discussed in the adverse event monitoring protocol [23] and procedures in case of pregnancies were established [24], so it is reasonable to assume a that certain proportion of patients were sexually active. Prolonged treatment into adulthood may well increase the relevance of such concerns.

To our knowledge, this is the first systematic assessment of adverse effects reporting in publications from the TADS study. We conducted an extensive literature search and believe that all relevant studies have been identified, however we cannot exclude the possibility that some publications may have been overlooked. Our findings regarding adverse effect reporting and potential for bias are based on analysis of only one study and do not give information on adverse effects reporting or bias in other studies of SSRIs in adolescents. However, discrepancies and weaknesses in the reporting of adverse events in such studies has also been noted by other authors [25 26].We have not had access to primary data.

A previous assessment of the adverse effects reporting in TADS focused on the occurrence of suicidal events and increased risk of suicidal behaviour [10] and this is reflected in the most recent Cochrane review.[1] Like Högberg et al,[10] we have noted the misleading placebo group classification of patients with a suicidal event who were using FLX at the time. Our analysis encompasses all adverse events mentioned in publications from the TADS study. Gaps and discrepancies in coding, transcription and reporting of harms in clinical trials have been reported, and the number of adverse events may differ between study reports and published papers.[25 27] Several barriers to accurate harms reporting [25] are relevant to the TADS study, notably the severity threshold, conversions from continuous to dichotomous outcomes, individual judgments of association between event and medication, handling of adverse events in patients who discontinued treatment, and the extensive use of concomitant medications. In future studies, the potential for bias may be substantially reduced by avoiding severity thresholds and defining a consistent method of describing adverse effects such as suicidal risk and mania score worsening. Occurrence or worsening of mania and other psychiatric adverse effects for individual patients should be reported in more detail. We would also suggest that if risk is presented as percentages, it should be calculated based on the number of patients who were receiving treatment at the time the adverse event occurred. This will be of particular importance in studies with large dropout rates and treatment changes. The full spectrum of

adverse effects should be reported for all study stages. A plan for data sharing should be in place to facilitate reanalysis and evaluation by other researchers, as practiced by the BMJ.[28]

Due to its long duration (36 weeks) and follow-up (1 year), the TADS study could have provided valuable information on the long-term occurrence of adverse effects both in frequency and severity. The adverse effects profile of fluoxetine in the TADS study has only been reported in detail for stage 1, where approximately 200 patients received fluoxetine for 12 weeks. The raw data from the trial have been requested [29] and planned for release into the public domain,[30] but we have not been able to ascertain that these have been made publicly available. The incomplete reporting of adverse effects in a major study like TADS may lead to bias and erroneous conclusions regarding the safety profile of fluoxetine when given to minors. The risk of suicidal behaviour has been the subject of many discussions and regulatory actions, but there has been considerably less focus on other clinically important adverse effects. This may have clinical important implications, since the benefit/risk estimations regarding fluoxetine use in adolecents will be biased. If adverse effects are not acknowledged as such, there is a risk that symptoms may be misinterpreted and treated as more serious illnesses.

Figure legend:
Figure 1 Selection and characteristics for publications from the TADS study

Contributors SN suggested the research question. All authors discussed and defined the project. TW and SN researched the literature and made the initial assessments. All authors discussed the publications included in the study, including interpretation and presentation of results. TW drafted and finalized the manuscript as lead author. SN and MK commented on the draft and revised the manuscript at all stages. All authors agreed to the final version of the manuscript.

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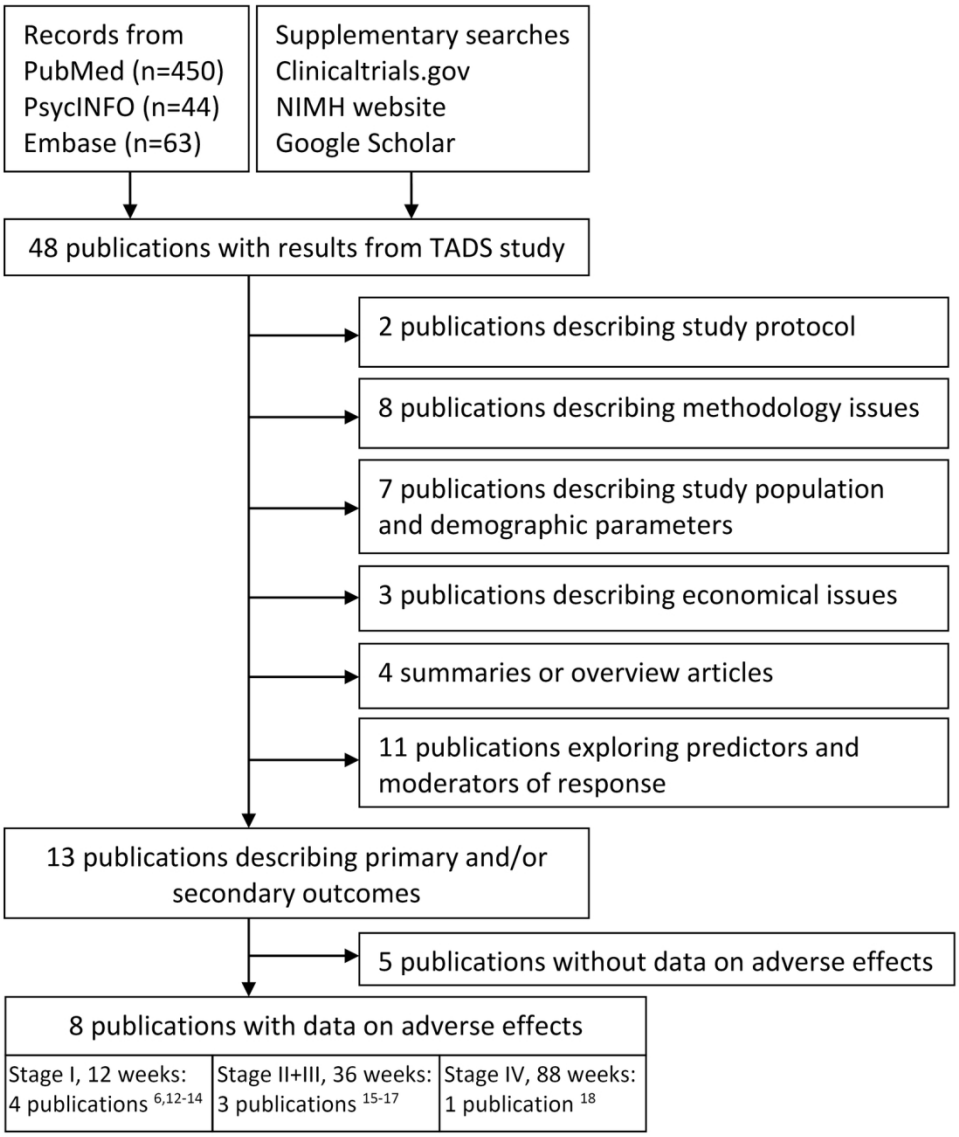

Figure 1 Selection and characteristics for publications from the TADS study

143x168mm (300 x 300 DPI)

Supplementary file. Reporting of suicidality in publications from the TADS study

Reporting parameter		Stage 1 (12 weeks)				Stage 2+3 (36 weeks)			Stage 4 (88 weeks)
		TADS 2004[6]	Emslie[12]	Kennard[13]	May[14]	TADS 2007[15]	Kennard[16]	Vitiello[17]	TADS 2009[18]
CDRS-R Item 13	% patients CDRS-R Item 13 score ≥2	Baseline: 27% 12 wk: 9.4%							
	% patients CDRS-R Item 13 score ≥6	Baseline: 2%							
	% patients CDRS-R Item 13 score ≥3		Baseline: 21.4%						
	% patients worsening CDRS-R Item 13 ≥1 point		COMB 5% FLX 13.4% CBT 15.2% PBO 7.2%						
	% patients increase CDRS Item 13 from 1-2 to ≥ 5		COMB 0 FLX 3.7% CBT 1.3% PBO 2.6%						
SIQ-Jr	% patients SIQ-Jr score ≥ 31	Baseline: 29% 12 wk: 10.3%	Baseline: 29.2%			Baseline: 97/320 (30.3%) FLX 28/107 (26.2%) COMB 42/106 (39.6%) CBT 27/107 (25.2%) **Stage 1 (12 wk)** **Completed score** / **Observed cases** All: 31/278 (11.2%) / All: 24/257 (9.3%) COMB 8/90 (8.9%) / COMB 5/84 (6.0%) FLX 18/97 (18.6%) / FLX 14/89 (15.7%) CBT 5/91 (5.5%) / CBT 5/84 (6.0%) **Stage 3 (36 wk)** All: 15/228 (6.6%) / All: 10/171 (5.8%) COMB 2/79 (2.5%) / COMB 0/63 (0%) FLX 10/73 (13.5%) / FLX 8/55 (14.5%) CBT 3/76 (3.9%) / CBT 2/53 (3.8%)			Baseline: COMB 1/78 (1.3%) FLX 4/73 (5.5%) CBT 0/76 (0%)
	% patients SIQ-Jr score increase to ≥ 31		All: 4.8% (18/374) COMB 2.2% (2/93) FLX 7.3% (7/96) CBT 2.2% (2/93) PBO 7.6% (7/92)						All: 6.4% COMB 5.9% FLX 7.6% CBT 6.4%
	SIQ-Jr score adjusted mean ±SD	Baseline: COMB 27.33 (18.51) FLX 21.81 (14.44) CBT 21.91 (16.28) PBO 24.20 (16.46) 12 wk: COMB 11.79 (11.69) FLX 14.44 (11.13) CBT 11.40 (10.44) PBO 15.01 (11.05)	12 wk: COMB 10.9 ± 0.3 FLX 13.7 ±0.2 CBT 11.3 ±0.3 PBO 14.5 ± 0.6						36 wk: COMB 10.2 ± 8.8 FLX 12.1 ± 11.1 CBT 9.5 ± 9.1 88 wk: COMB 9.3 ± 7.8 FLX 10.5 ± 10.4 CBT 8.2 ± 8.1

Supplementary file. Reporting of suicidality in publications from the TADS study, cont'd.

Reporting parameter		Stage 1 (12 weeks)				Stage 2+3 (36 weeks)			Stage 4 (88 weeks)
		TADS 2004[6]	Emslie[12]	Kennard[13]	May[14]	TADS 2007[15]	Kennard[16]	Vitiello[17]	TADS 2009[18]
Number of cases	Harm-related AE†	All: 33/439 (7.5%) Serious: 23/33 (69.7%) COMB 9/107 (8.41%) FLX 13/109 (11.93%) CBT 5/111 (4.50%) PBO 6/112 (5.36%)							
	Suicide-related AE†	All: 24/439 (5.5%) COMB 6/107 (5.61%) FLX 9/109 (8.26%) CBT 5/111 (4.50%) PBO 4/112 (3.57%)	24 (5.5%) COMB 5 (4.7) FLX 10 (9.2%) CBT 5 (4.5%) PBO 3 (2.7%)		16/78				
	Suicidal event†					**Stage 1 (12 wk)** **Observed cases** / **Intention-to-treat** All: 20/327 (6.1%) / All: 22/327 (6.7%) COMB 5/107 (4.7%) / COMB 5/107 (4.7%) FLX 10/109 (9.2%) / FLX 12/109 (11.0%) CBT 5/111 (4.5%) / CBT 5/111 (4.5%) **Stage 3 (36 weeks)** All: 26/327 (8.0%) / All: 32/327 (9.8%) COMB 8/107 (7.5%) / COMB 9/107 (8.4%) FLX 12/109 (11.0%) / FLX 16/109 (14.7%) CBT 6/111 (5.4%) / CBT 7/111 (6.3%)	**Stage 2-3 (12-36 wk)** PBO/Open 10.7% (12/112) Active 32/327 (9.8%)	All: 44/439 (10.0%) COMB 9/107 (8.4%) FLX 16/109 (14.7%) CBT 7/111 (6.3%) (5 CBT, 2 FLX at event) PBO 12/112 (10.7%) (3 PBO, 9 FLX at event) SSRI at event: 36	
	Suicidal. inc. self-harm				27/78 (37.6%)				
	Thoughts self-harm				8/27 (29.6%)				
	Plan self-harm				8/27 (29.6%)				
	Intent self-harm				4/27 (14.8%)				
	Attempt self-harm				All: 7/27 (25.9%) COMB 1 FLX 4 CBT 1 PBO 1				
	Intend, plan, attempt self-harm				All: 16 COMB 3 FLX 7 CBT 3 PBO 4				
	Intend, plan, attempt suicide (Columbia reassess.)				All: 9 COMB 2 FLX 3 CBT 2 PBO 2				

Supplementary file. Reporting of suicidality in publications from the TADS study, cont'd.

Reporting parameter		Stage 1 (12 weeks)				Stage 2+3 (36 weeks)			Stage 4 (88 weeks)
		TADS 2004[6]	Emslie[12]	Kennard[13]	May[14]	TADS 2007[15]	Kennard[16]	Vitiello[17]	TADS 2009[18]
Number of cases	Suicidal ideation†		All: 18 (4.1%) COMB 3 (2.8%) FLX 8 (7.3%) CBT 4 (3.6 %) PBO 3 (2.7%)	6/129 (remitters, from fig.)				All 23/439 (5.2%)	
	Suicide-related AE, Columbia 1,2,6†		All: 23 (5.2%) COMB 5 (4.7%) FLX 10 (9.2%) CBT 5 (4.5%) PBO 3 (2.7%)						
	Suicide-related AE, Columbia 1,2,3,6†		All: 24 (5.5%) Serious: 15 COMB 6 (5.6%) FLX 10 (9.2%) CBT 5 (4.5%) PBO 3 (2.7%)						
	Attempt suicide†	All: 7/439 (1.6%) COMB 4 FLX 2 CBT 1	All: 5 COMB 2 FLX 2 CBT 1 PBO 0					All 21/439 (4.8%)	

† Frequency calculations based on ITT groups

ENTREQ Checklist

Critical appraisal of adverse effects reporting in the "Treatment for Adolescents With Depression Study (TADS)" study. Westergren et al.

No	Item	Guide and description
1	Aim p.6	Background:The "Treatment for Adolescents With Depression Study (TADS)" study was performed in 2000-2003. The study included 439 youths who were randomized to treatment with fluoxetine, cognitive behavioral therapy, cognitive behavioral therapy plus fluoxetine, or placebo. The study is regarded as a high-quality study and is referred to in most systematic reviews and treatment recommendations on the effectiveness and risk of antidepressant therapy in adolescents. Objective: To identify all publications from the TADS study and assess the publications with regard to reporting of adverse effects in the treatment groups both for the short-term and long-term study stages.
2	Synthesis methodology p.6	Descriptive (whether adverse effects were presented and which adverse effects were presented)
3	Approach to searching p.6	a) Pre-planned search, with a comprehensive search strategy b) Snowball search
4	Inclusion criteria p.6-7	All available studies arising from the TADS study, assessed for mention of adverse effects
5	Data sources p.6	Searches in PubMed, EMBASE, Psychinfo, Google Scholar, clinicaltrials.gov, National Institute of Mental Health website nimh.nih.gov, the Duke Clinical Research Institute TADS website http://tads.dcri.org, hand searching of references in identified publications, and by searching other publications by the main authors. Searches conducted June 2017-February 2018. An additional literature search in PubMed for any recent TADS publications was

No	Item	Guide and description
		updated in January 2019. Rationale for using the data sources: Known publications found in PubMed and EMBASE. One treatment arm was for cognitive therapy, and it was possible that there publications could be found in PsychInfo.
6	Electronic Search strategy p.6	Search terms in Google Scholar were either «TADS team» or «Treatment for adolescents with depression study». Search term in PsycINFO was «Treatment for adolescents with depression study». Search term in PubMed was the phrase Treatment for adolescents with depression study. The initial publications with data from the TADS study were identified and used to search for similar publications, limited from 2004 to 1. September 2017, Clinical Trial or Randomized Controlled Trial and age group Child 0-18. Search term in Embase was «Treatment for adolescents with depression study».
7	Study screening methods p.7	Authors TW and SN reviewed study abstracts to identify publications from the TADS study. All identified studies were reviewed in full text to assess whether they reported adverse effects.
8	Study characteristics p.7	All included publications refer to the same study: The "Treatment for Adolescents With Depression Study (TADS)" study. Included studies refer to different study stages or study populations and were published from 2004-2009.
9	Study selection results p.7	We screened 48 TADS publications and excluded 40 for not providing any information on adverse effects. The selection process in described in Figure 1.
10	Rationale for appraisal p.7	We intended to identify any TADS publication that gave some information on adverse effects, without further quality assessment or limitations, in order to include all possibly relevant data.

No	Item	Guide and description
11	Appraisal items	See over
12	Appraisal process p.7	Appraisal was conducted independently by two reviewers. Appraisal was discussed bya third reviewer in case of doubt or disagreement.
13	Appraisal results p.7	No articles identified as giving information on adverse effects were excluded for quality or other reasons.
14	Data extraction p.7	All adverse effects mentioned in text or tables were included in overview tables.
15	Software	No analysis computer software
16	Number of reviewers p.7	Tone Westergren, Sigrid Narum, Marianne Klemp.
17	Coding	No coding
18	Study comparison p.7	Adverse effects reported or referred to as described in original studies, without recoding
19	Derivation of themes	Not relevant; Descriptive process
20	Quotations	Not relevant

No	Item	Guide and description
21	Synthesis output p.12-14	Our findings raise the question of whether this central study, and the large number of publications arising from it, has generated a perception that adverse effects of fluoxetine were well documented both in short-term and long-term treatment. In fact, the risk/benefit assessments during the later study stages narrowed the risk factors down to one factor only; the risk of suicidal events. Other, more common, adverse effects are not part of the total risk assessment in short- or long-term use, thereby skewing the perceived risk/benefit relationship.