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Suicidality and self-injury with selective serotonin reuptake inhibitors in youth: Occurrence, predictors and timing

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Abstract

Objective: Meta-analyses have established a heightened risk of suicidality for youth treated with selective serotonin reuptake inhibitors (SSRIs). The present study investigates the risk and possible predictors of suicidality and non-suicidal self-injury (NSSI) associated with SSRI treatment in a clinical sample of children and adolescents.

Methods: An observational, longitudinal, retrospective study using a within-subject study design including in- and outpatients aged 0–17 years treated with SSRIs. Data were obtained from digital medical records and prescription software.

Results: $N = 365$ patients were included (64.1% female), mean (SD) age 14.5 (2.04) years, with primary depression, anxiety or obsessive-compulsive disorder. No suicides occurred. When comparing the 6-week period immediately prior to versus following SSRI initiation, the patient proportion with broadly defined suicidality decreased (38.5% vs. 24.2%, $p < 0.001$) while the proportion with suicide attempts was stable (2.8% vs. 2.8%, $p = 1.000$). The proportion with NSSI decreased statistically non-significantly (12.4% vs. 8.4%, $p = 0.067$). Results from individually standardized observation periods were similar; however, the proportion with suicide attempts decreased statistically non-significantly and the proportion with NSSI decreased significantly. Suicidality during SSRI treatment was associated with previous suicidality (OR[CI] = 6.0 [2.4–14.8], $p < 0.001$), depression as indication for SSRI treatment (OR[CI] = 2.1 [1.2–3.7], $p = 0.01$), female sex (OR[CI] = 2.1 [1.1–4.1], $p = 0.02$) and previous NSSI (OR[CI] = 2.0 [1.2–3.5], $p = 0.01$).

Conclusion: Suicidality was common in youth treated with SSRIs. The patient proportion with overall suicidality decreased, and the proportion with attempted suicide was stable in the weeks following SSRI initiation. Previous suicidality, depression, female sex and previous NSSI are important predictors for suicidality during SSRI treatment in youth.

KEYWORDS
adolescents, children, non-suicidal self-injury, serotonin reuptake inhibitors, suicidality

1 | INTRODUCTION

The wide use of antidepressants for children and adolescents[1] has been debated due to questions about safety. Several meta-analyses of data from randomized controlled trials (RCTs) have found an increased risk of suicidal behaviour and ideation (suicidality) for children and adolescents during antidepressant treatment.[2–7] Meta-analyses suggest an increased risk of suicidal ideation or behaviour in the range of 7–20 incidents per 1,000 patients treated with antidepressants compared with placebo.[3] These findings have led to warnings by the authorities about the use of antidepressants for children and adolescents.[8–10] However, the decision by the authorities has been criticized for a number of reasons: no suicides were observed in any of the trials included in the meta-analyses; the trials were not designed to investigate suicide risk; and the concept of 'suicidality' is imprecise.[11] In many trials, patients with suicidality and patients with comorbid disorders were excluded, thus complicating extrapolation to a clinical population.[2,6] Furthermore, following the US warnings, a decrease in prescription of antidepressants coincided with an increase in suicide attempts among adolescents[12] and pharmaco-epidemiological studies have shown an inverse relationship between antidepressant use and suicide rates for children and adolescents.[3] However, in a meta-analysis of observational studies, exposure to selective serotonin reuptake inhibitors (SSRIs) increased the risk of suicide or suicide attempt among adolescents.[13]

The relationship between antidepressants and suicidality is complex. Depression is a strong risk factor for suicide attempt in children and adolescents; in fact, mental illness of most diagnostic groups is associated with a heightened risk of suicide attempt[14] and suicidal behaviour often promotes clinicians to initiate antidepressant treatment.[15] It is therefore difficult to distinguish an antidepressant emergent risk of suicidality from a persistent risk present before and after the treatment initiation, when treating children and adolescents with antidepressants in the clinic.

An important question is whether SSRI-related suicidality primarily occurs in vulnerable individuals and, if so, what specific factors are associated with suicidality during SSRI treatment. Predictors for suicidality in children and adolescents are comprehensively described,[14,16,17] and less is known about predictors for suicidality during antidepressant treatment. Kuba et al.[18] investigated predictors for suicide-related events (suicidal ideation, self-injury and suicide attempt) in a cohort of 70 patients (6–19 years) across indications during the first 3 months of antidepressant treatment and found that patients with risk of suicidality during antidepressant treatment were characterized by female sex, psychotic features, borderline personality disorder, previous suicidality and baseline psychopathology such as anhedonia, irritability and hopelessness. Other studies have mainly focused on predictors for suicidality in samples of depressed adolescents[19–21] in which predictors of suicidality during treatment were found to be high suicidality, non-suicidal self-injury (NSSI), severity of depressive symptoms, family conflict/poor family function and drug or alcohol use.[19–21] Data from RCTs may suggest that antidepressants increase the risk of suicidality in children and adolescents when the indication is major depressive disorder, but not for other indications.[22] Others argue that there is not enough data on other indications than depression to make firm conclusions.[23]

Another important question is in what time period relative to SSRI initiation the risk of suicidality is increased. National guidelines[24] and 'clinical knowledge' state that patients are at heightened risk of suicide as they begin to recover from depression because the motor inhibition of depression resolves before other depressive symptoms have resolved, although this theory lacks supporting evidence.[25] The meta-analyses referred to above do not provide

Significant outcomes

- The risk of suicidality decreased after SSRI initiation in this clinical sample of children and adolescents.
- Suicidality during SSRI treatment is predicted by previous suicidality, depression as indication for SSRI treatment, female gender and previous non-suicidal self-injury.

Limitations

- Due to the retrospective design, the accuracy of the assessment of outcome depends on the information entered in the medical record when clinicians routinely monitor for suicidality and self-injury or the patient spontaneously reports events. Healthcare providers in Denmark are liable to record information about patients' conditions and treatment.
- Data were collected by two researchers. Interrater reliability of classification of suicidality and non-suicidal self-injury was not assessed which may cause inaccuracies.
- The lack of a non-SSRI control group limits the interpretation of the results.

analyses on timing of suicidality events. The study duration of the RCTs included in the meta-analyses ranged from 4 to 19 weeks.[2–7] The timing of suicidality occurring during antidepressant treatment has been investigated in two trials with depressed adolescents: In the Treatment of Adolescent Depression study (TADS) trial, suicidal events occurred from few days after treatment initiation and were not less frequent in the second month compared with the first, mean time to first suicidal event was 9.1 weeks ± SD 23.3 weeks[19]; in the Treatment of Resistant Depression in Adolescents (TORDIA) trial, the median time from antidepressant initiation to a suicidal event occurred was 3 weeks.[21] From other studies, it seems that the risk of suicide or suicide attempt is highest in the period immediately prior to antidepressant initiation.[15,26] Moreover, the risk appears to be increased during periods of titration and during the discontinuation period for patients of all age groups.[27]

Although randomized controlled trials (RCTs) are the gold standard for investigating treatment effects, certain suicidality events, such as suicide attempts, are rare, and therefore, large patient samples should be investigated. However, pharmacological trials in youth are usually not powered to capture differences in seldom events, and therefore, evidence is based on meta-analyses in which a great variability in care and observation measures is inherent. Furthermore, most RCTs do not consider the level of suicidality prior to SSRI initiation. In a published study of the present sample, we found that in a large majority of the 365 cases of children and adolescents treated with SSRI, the clinicians complied with recommendations from clinical guidelines regarding managing and monitoring the risk of suicidality.[28] We therefore decided that this large cohort of youths was suitable for further studying the risk of suicidality associated with SSRI treatment.

1.1 | Aims of the study

The present study aims to describe suicidality and nonsuicidal self-injury (NSSI) in a naturalistic setting in a large sample of children and adolescents treated with antidepressants (more specifically selective serotonin reuptake inhibitors (SSRIs)) across psychiatric indications using a within-subject study design. The study investigates the prevalence and week by week risk for suicide, suicidal behaviour, suicidal ideation and self-injury along with possible predictors for suicidality during SSRI treatment of children and adolescents.

2 | METHODS

2.1 | Study design and source of information

The study used a retrospective and longitudinal design in a sample of children and adolescents affiliated with Child and Adolescent Mental Health Services (CAMHS), Capital Region, Denmark. The patients were identified via electronic prescription software (PLISS) used for all prescriptions in CAMHS. All patients have a unique id-number which was used to extract data from the digital medical record (OPUS) and the electronic medicine monitoring system (EPM). Clinicians enter information about patient symptoms, diagnoses and treatment in the digital medical record after each patient contact, and all medicines are prescribed by clinicians via the medicine monitoring system.

We followed the STROBE statement for reporting observational studies.[29]

2.2 | Setting

Patients with a prescription for an SSRI were identified by one researcher (TR) in June 2016. Two researchers (JØS and AR) searched the medical records and the medicine monitoring system for relevant clinical data using a detailed data abstraction form. Data were extracted manually in July–September 2016 in The Research Unit, CAMHS, Capital Region of Denmark.

2.3 | Participants

All in- and outpatients aged 0–17 years with a recorded prescription for an SSRI classified within ATC group N06AB undergoing treatment at the CAMHS on January 1st, 2016 (index date).

Patients aged 18 years and above on the date of SSRI initiation and patients who were not undergoing SSRI treatment on index date according to the medical record were excluded. Patients for whom SSRI treatment was not initiated in CAMHS (i.e., SSRI treatment was initiated in a private child- and adolescent psychiatric practice, or another practitioner, not part of CAMHS) were excluded because not all clinical information was available in the CAMHS medical records. For the same reason, patients in which it was impossible to determine who initiated the SSRI treatment were excluded. Patients who had another recorded prescription for SSRI prior to the SSRI which was prescribed on index date were excluded.

2.4 | Data

Date of study entry was defined as the first entry in the course of treatment that included the SSRI prescription valid on January 1st, 2016. End of follow-up was defined as 6 months after SSRI treatment initiation or until the patient was no longer a patient in CAMHS, whichever came first. The observation periods varied between patients because of the naturalistic design of the study. Age and admission status were registered as it was on SSRI initiation date. Psychiatric diagnoses were included according to ICD-10.[30] Since diagnoses could be changed during the study period, diagnoses from an entry immediately before or on the initiation date were extracted. Tentative diagnoses were included if a firm diagnosis was not yet established. Every event entered in the medical records with potential suicidality were counted and classified using The Columbia Classification Algorithm of Suicide (C-CASA).[31] C-CASA classifies events into eight categories: Suicide; Suicide attempt; Preparatory acts towards imminent suicidal behaviour; Suicidal ideation; Self-injurious behaviour, Self-injurious behaviour, no suicidal intent; Self-injurious behaviour, intent unknown; Other, no deliberate self-injury; Not enough information. Suicide, suicidal attempts, preparatory acts and ideation are categorized as suicidality. Self-injurious behaviour with no suicidal intent and other deliberate self-injury are categorized as NSSI. Self-injurious behaviour with unknown intent and events with insufficient information are categorized as indeterminate events. All events were registered with date making it possible to determine the time relative to SSRI initiation date. If two events occurred on the same date, events were registered hierarchically according to severity. A suicide attempt was thus only registered as suicide attempt and not as preparatory acts or suicidal ideation even though these events had occurred related to the suicide attempt on the same date. The severity hierarchy was as follows: suicide attempt > preparatory behaviour > suicidal ideation.[31] If events of suicidality and non-suicidality occurred on the same date both events were registered in different categories. To account for the risk of misclassification, doubts regarding the classification of suicidality events were conferred with a senior consultant and specialist in child and adolescent psychiatry (AKP).

2.5 | Statistical analysis

Statistics were performed using IBM Corp, IBM SPSS Statistics for Windows Version 25.0. The Mann-Whitney U Test was applied to test for statistically significant age difference between males and females. The Pearson χ^2-test was used to test for differences between children and adolescents according to gender, admission status, type of SSRI, indication and medication status along with differences in the risk of suicidality according to non-pharmacological interventions and admission status. The McNemar-test was used to test for differences between the risk for an individual to have at least one event of suicidality or NSSI before and after the initiation of SSRIs. To test for the difference in the total number of events before and after SSRI initiation, a poisson log linear regression using generalized estimating equations model with robust standard errors was used. A threshold of $p < 0.05$ was used for statistical significance. Because the risk periods preceding and following SSRI initiation were not equal within or between patients, the observation periods were standardized for each patient. The duration of the time period prior to and following SSRI initiation was estimated for each individual and adjusted to be equal in length, that is, as long as the shortest of the two periods. Hereafter, these periods are referred to as 'standardized observation periods'. Possible predictors were tested in a logistic regression analysis using a stepwise backward (Wald) method with any suicidality within 6 weeks after SSRI initiation as the dependent variable and the following variables as covariates: gender (male vs. female), age (children vs. adolescents), indication (depression vs. other), co-morbidity vs. no co-morbidity, previous suicidality vs. no previous suicidality and previous self-injurious behaviour vs. no. previous self-injurious behaviour.

2.6 | Ethical aspects

The study was approved by the Danish Data Protection Agency (journal no.: 2012–58–0004) and the Danish Patient Safety Authority (journal no. 3–3013-1554/1+2/). Informed consent from patients and caretakers was not demanded. Approval from the Ethics Committee was not required according to Danish Law.

3 | RESULTS

In total, 5410 patients were associated with CAMHS on January 1st, 2016. Out of 530 patients identified as SSRI-users on initiation date, 365 patients were eligible for study inclusion. Table 1 summarizes patient characteristics. The majority (64.1%, $n = 234$) was female. Mean (SD) age was 14.5 (2.04) years, ranging from 7.7 to 17.9 years and was statistically significantly higher for females than for males, (14.8 [1.8] years vs. 13.6 [2,2] years, $p < 0.001$). More patients were adolescents (aged 14–17) compared with children (aged 0–13) (64.7%, $n = 236$ vs.

TABLE 1 Characteristics of study population. $N = 365$

	No. of patients (%)	Children (%)	Adolescents (%)	$p^{\dagger}$
Adolescents (14–17 years)	236 (64.7%)			<0.001
Children (7–13 years)	129 (35.3%)			
Gender				
Female	234 (64.1%)	59 (45.7%)	175 (25.8%)	
Male	131 (35.9%)	70 (54.3%)	61 (74.2%)	<0.001
Patient status at SSRI initiation				
Outpatient	284 (77.8%)	92 (71.3%)	192 (81.4%)	
Inpatient	81 (22.2%)	37 (28.7%)	44 (18.6%)	0.35
Drug				
Sertraline	280 (76.7%)	113 (87.6%)	166 (70.3%)	
Fluoxetine	84 (23.0%)	16 (12.4%)	69 (29.2%)	
Citalopram	1 (0.3%)	0	1 (0.4%)	0.001
Indication for SSRI				
Depression	147 (40.3%)	31 (24.0%)	116 (49.2%)	
Anxiety	108 (29.6%)	39 (30.2%)	69 (29.2%)	
OCD	87 (23.8%)	51 (39.6%)	36 (15.3%)	
Depression and anxiety	9 (2.5%)	2 (1.6%)	7 (3.0%)	
Anxiety and OCD	6 (1.6%)	2 (1.6%)	4 (1.7%)	
Depression and OCD	3 (0.8%)	2 (1.6%)	1 (0.4%)	
Depression, anxiety and OCD	2 (0.5%)	1 (0.8%)	1 (0.4%)	
'Nerve medicine'	2 (0.5%)	1 (0.8%)	1 (0.4%)	
PTSD and anxiety	1 (0.3%)	0	1 (0.4%)	<0.001
Number of diagnoses				
1	104 (28.5%)	37 (28.7%)	67 (28.4%)	
2	142 (38.9%)	46 (35.7%)	96 (40.7%)	
3	90 (24.7%)	34 (26.4%)	56 (23.7%)	
4	24 (6.6%)	10 (7.8%)	14 (23.7%)	
5	5 (1.4%)	2 (1.6%)	3 (1.3%)	
Other drugs at SSRI initiation				
No	218 (59.7%)	69 (53.5%)	149 (63.1%)	
Yes	147 (40.3%)	60 (46.5%)	87 (36.9%)	0.075
Other drugs at SSRI initiation				
Melatonin	93 (25.5%)			
Quetiapine	19 (5.2%)			
Olanzapine	16 (4.4%)			
Chlorprothixene	13 (3.6%)			
Methylphenidate	13 (3.6%)			
Aripiprazole	10 (2.7%)			
Oxazepam	9 (2.5%)			
Risperidone	9 (2.5%)			
Atomoxetine	4 (1.1%)			
Lisdexamfetamine	2 (0.5%)			
Valproate	2 (0.5%)			
Lamotrigine	2 (0.5%)			

(Continues)

TABLE 1 (Continued)

	No. of patients (%)	Children (%)	Adolescents (%)	$p^{\dagger}$
Clonidine	1 (0.3%)			
	Range	**Mean (SD)**	$p^{\ddagger}$	
Age, all (years)	[7.7–17.9]	14.5 (2.04)		
Age, females (years)	[7.7–17.9]	14.8 (1.8)		
Age, males (years)	[9.3–17.6]	13.6 (2.2)	<0.001	
	Start dose (Mean [SD])	**Maintenance dose (Mean [SD])**	**Max dose (Mean [SD])**	
Doses in mg				
Sertraline	12.5–50 (27.3 [8.0])	25–200 (105.3 [46.6])	25–200 (110.0 [45.3])	
Fluoxetine	10–20 (10.9 [2.9])	10–40 (25.4 [7.0])	10–40 (26.7 [7.9])	
Citalopram	10	10	20	

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

[†]Comparison of age groups. Pearson's chi-square test was used to test for significance.

[‡]Comparison of mean age by sex. Mann-Whitney U test was used to test for significance.

35.5%, $n = 129$, $p < 0.001$). Most patients were outpatients (77.8%, $n = 284$, $p < 0.001$). Sertraline was the most common SSRI (76.7%, $n = 280$), followed by Fluoxetine (23.0%, $n = 84$). Only 0.3% ($n = 1$) of patients received Citalopram. The most common indication for SSRI treatment was depression (40.3%, $n = 147$) followed by anxiety (29.6%, $n = 108$) and obsessive-compulsive disorder (OCD) (23.8%, $n = 87$). The mean observation period before SSRI initiation was 228.3 days (327.4), ranging from 0 to 2610 days and the mean observation period from SSRI initiation to end of follow-up was 167.4 days (20.5), ranging from 8 to 185 days.

3.1 | Occurrence

There were no suicides in the study. In the period from study entry to SSRI, a total of 1219 events occurred in 268 patients (73.4%) with 913 suicidality events in 253 patients (69.3%) and 268 NSSI events in 110 patients (30.1%). To account for NSSI being categorized as suicidality in previous literature,[2] the risk of having at least one event of either of NSSI or suicidality was calculated and was 72.9% ($n = 265$). In the period from SSRI initiation until end of follow-up, a total of 1,028 events occurred in 179 patients (49.0%), 735 suicidality events occurred in 150 patients (41.1%), 261 NSSI events in 75 patients (20.5%) and 166 patients (45.5%) had at least one event of either suicidality or NSSI. The numbers from the entire observation period are shown in Table S1.

The standardized observation periods ranged from 0 to 185 days, mean (SD) 114.45 (54.8) days. Results on the occurrence of suicidality and NSSI in the standardized periods are shown in Table 2. In the standardized observation period prior to SSRI initiation, 763 events occurred in 221 patients (60.5%), 609 suicidality events in 202 patients (55.3%), 135 NSSI events in 70 patients (19.2%), and an event of either suicidality or NSSI occurred in 216 patients (19.2%). In the standardized time period following SSRI initiation, 651 events occurred in 148 patients (40.5%), 468 suicidality events occurred in 125 patients (34.2%), 162 NSSI events occurred in 44 patients (12.1%) and an event of either suicidality or NSSI occurred in 137 patients (37,5%). The decrease in risk from the time period prior to SSRI initiation vs. the time period following SSRI initiation was statistically significant for all events ($p < 0.001$), suicidality ($p < 0.001$), NSSI (0.002) and either suicidality or NSSI ($p < 0.001$). The decrease in suicidality following SSRI initiation was driven mainly by a decrease in suicidal ideation from 564 events in 195 patients (53.4%) to 468 events in 122 patients (34.2%, $p < 0.001$). For the number of events, there was statistically significantly fewer suicidality events ($p = 0.010$) and events of suicidal ideation ($p = 0.005$) in the period following SSRI initiation compared with the period before initiation ($p = 0.010$). The number of suicide attempts increased from 22 attempts to 33 attempts, but this finding was statistically non-significant ($p = 0.328$). The same applied for NSSI events ($p = 0.334$).

To analyse the risk of events in the period immediately following SSRI initiation, the observation periods were standardized to 6 weeks immediately prior to and 6 weeks immediately following SSRI initiation. The results are shown in Table 3. Patients who were not observed in both periods were excluded from the analyses, leaving 322 cases to be analysed. The excluded individuals were observed prior to SSRI initiation in the range of 0–41 days (mean [SD] 22.98 [12.5] days) prior to and in the range of 64–184 days

TABLE 2 Occurrence of suicidality and NSSI in standardized periods before and after SSRI initiation. $N = 365$

	Before[‡]		After[‡]		Tests for significance			
Event type	**No. of events**	**Patients (%[†])**	**No. of events**	**Patients (%[†])**	**Intercept[¶]**	**β[¶]**	**p[¶]**	**p[§]**
Any event	763	221 (60.5)	651	148 (40.5)	0.579	0.159	0.123<0.001	
Suicidality	609	202 (55.3)	468	125 (34.2)	0.249	0.263	0.010	<0.001
Suicide attempt	22	19 (5.2)	33	16 (4.4)	−2.403	−0.405	0.328	0.678
Preparatory act	23	20 (5.5)	14	12 (3.3)	−3.261	0.496	0.151	0.186
Suicidal ideation	564	195 (53.4)	421	122 (33.4)	0.143	0.292	0.005	<0.001
NSSI	135	70 (19.2)	162	44 (12.1)	−0.812	−0.182	0.334	0.002
Self-injury, no suicidal intent	135	70 (19.2)	161	43 (11.8)	−0.818	−0.176	0.353	0.001
Other, no deliberate self-injury	0	0	1	1 (0.3)	-	-	-	1
Indeterminate, any	19	18 (4.9)	21	19 (5.2)	−2.855	−0.100	0.751	1
Self-injurious behaviour, Unknown intent	7	7 (1.9)	9	8 (2.2)	−3.703	−0.251	0.634	1
Not enough information	12	12 (3.3)	12	11 (3.0)	−3.415	−1.094E−14	1	1

Note: Standardized period: The duration of the time period prior to and following SSRI initiation was estimated for each individual and adjusted to be equal in length, that is, as long as the shortest of the two periods.

Abbreviations: NSSI, Non-Suicidal Self-Injury; SSRI, selective serotonin reuptake inhibitor.

[†]Of total population observed in the period.

[‡]Before and after the initiation of SSRIs.

[¶]Possion log linear regression model using generalized estimating equations was used to test for significance of the differences in number of events.

[§]Mcnemar's test was used to test for significance of the difference in risk of at least one event.

TABLE 3 Occurrence of suicidality and NSSI in the 6 weeks before and the 6 weeks after SSRI initiation. $N = 322$

	Before‡		After‡		Tests for significance			
Event type	**No. of events**	**Patients (%†)**	**No. of events**	**Patients (%†)**	**Intercept¶**	**β¶**	**p¶**	**p§**
Any event	370	142 (44.1)	309	91 (28.3)	−0.041	0.180	0.162	<0.001
Suicidality	290	124 (38.5)	217	78 (24.2)	−0.395	0.290	0.020	<0.001
Suicide attempt	11	9 (2.8)	19	9 (2.8)	−2.830	−0.547	0.329	1.000
Preparatory act	7	7 (2.2)	7	6 (1.9)	−3.829	$7.094*10^{-16}$	1.000	1.000
Suicidal ideation	272	120 (37.7)	191	76 (23.6)	−0.522	0.354	0.005	<0.001
NSSI	71	40 (12.4)	86	27 (8.4)	−1.320	−0.192	0.418	0.067
Self-injury, no suicidal intent	71	40 (12.4)	86	27 (8.4)	−1.320	−0.192	0.418	0.067
Other, no deliberate self-injury	0	0	0	0	-	-	-	-
Indeterminate, any	9	9 (2.8)	6	5 (1.6)	−3.983	0.405	0.483	1.000
Self-injurious behaviour, Unknown intent	2	2 (0.6)	3	2 (0.6)	−4.676	−0.405	0.693	1.000
Not enough information	7	7 (2.2)3	3	3 (0.9)	−4.676	0.847	0.220	0.344

Abbreviations: NSSI, Non-Suicidal Self-Injury; SSRI, selective serotonin reuptake inhibitor.

†Of total population observed in the period.

‡Before and after the initiation of SSRIs.

¶Possion log linear regression model using generalized estimating equations was used to test for significance of the differences in number of events.

§Mcnemar's test was used to test for significance of the difference in risk of at least one event.

(mean [SD] 164.53 [25.9] days) following SSRI initiation. In the 6 weeks leading up to SSRI initiation, 370 events occurred in 142 patients, 290 suicidality events in 124 patients (38.5%), 71 NSSI events in 40 patients (12.4%) and an event of either suicidality or NSSI occurred in 138 patients (42.9%). In the 6 weeks following SSRI initiation, 309 events occurred in 91 patients (28.3%), 217 suicidality events in 78 patients (24.2%), 86 NSSI events in 27 patients (8.4%) and either an event of suicidality or NSSI event in 87 patients (27.0%). The decrease in risk from the time period immediately prior to SSRI initiation to the time period immediately following SSRI initiation was statistically significant for any event ($p < 0.001$), suicidality ($p < 0.001$) and suicidality or NSSI ($p < 0.001$), but statistically non-significant for the risk of NSSI ($p = 0.067$). Suicidal ideation decreased from 272 events in 120 patients (37.7%) to 191 events in 76 patients (23.6%, $p < 0.001$), while the number of suicide attempts was 11 attempts in 9 patients (2.8%) in the 6-week period before SSRI initiation and 19 attempts in 9 patients (2.8%, $p = 1.000$) in the 6-week period following SSRI initiation. For the number of events, there was a statistically significant decrease in suicidality events ($p = 0.020$) and suicidal ideation ($p = 0.005$ in the 6 weeks before vs. after SSRI initiation). The number of suicide attempts and events of NSSI increased, but this finding was statistically non-significant ($p = 0.329$ and $p = 0.418$), respectively.

The risk of events during SSRI treatment was affected by admission status. Inpatients had a higher risk of any event (56.8% vs. 35.9%, $p = 0.001$), suicidality (46.9% vs. 30.6%, $p = 0.008$) and NSSI (27.2 vs.7.7% $p > 0.001$). The same applied in the 6-week period immediately following SSRI treatment where the risk was higher for any event (49.3% vs. 22.7% $p > 0.001$), suicidality (28.8% vs. 20.4% $p = 0.001$) and NSSI (24.4% vs. 3.9% $p < 0.001$) for inpatients vs. outpatients. Treatment with non-pharmacological interventions prior to SSRI treatment did not affect the risk of events. The risk of events was higher for patients treated with non-pharmacological interventions in parallel with SSRI treatment vs. patients who did not receive parallel non-pharmacological treatment for any event (42.5% vs. 12.5%, $p = 0.004$) and suicidality (35.8% vs. 12.5% $p = 0.024$), but not NSSI ($p = 0.096$). The risk of events was not affected by parallel treatment with non-pharmacological interventions in the 6-week period immediately following SSRI initiation.

3.2 | Predictors

To identify possible predictors for suicidality during SSRI treatment, a logistic regression analysis was performed with suicidality within 6 weeks after SSRI initiation as the dependent variable and gender, age, indication, comorbidity, previous suicidality and previous NSSI as predictor variables. Table 4 gives the odds ratios (ORs) and the probability values for each of the predictors. This shows that previous suicidality (OR = 6.0, $p < 0.001$), depression as indication for SSRIs (OR = 2.1, $p = 0.01$), female gender (OR = 2.1, $p = 0.02$) and previous NSSI (OR = 2.0, $p = 0.01$) increase the risk of suicidality within the first 6 weeks after SSRI initiation.

3.3 | Weekly risk of suicidality relative to SSRI initiation

Figure 1 illustrates the number of patients who had at least one event of suicidality or NSSI week by week across a time interval of 6 weeks before and 3 months after SSRI initiation. Patients who were not observed in these periods were excluded from the timeline, leaving 321 cases to be analysed. The figure shows that the risk of suicidality peaks in the 2 weeks leading up to SSRI initiation and then sharply declines. The same time pattern applies for all events and patients with any event but not for NSSI.

4 | DISCUSSION

In this study, the occurrence, predictors and weekly risk of suicidality and NSSI were described in a clinical sample of 365 children and adolescents aged 7–17 years treated with SSRIs. The main findings are that suicidality was common in children and adolescents who need SSRI intervention, the risk of suicidality decreased after SSRI initiation and the risk of suicidality within the first 6 weeks after SSRI initiation was predicted by previous suicidality, depression as indication for SSRIs, female gender, and previous NSSI.

TABLE 4 Predictors with ORs for suicidality within 6 weeks after SSRI initiation. $N = 365$

Predictor	OR [CI]	*p*
Female sex	2.1 [1.1–4.1]	0.02
Depression as indication for SSRI	2.1 [1.2–3.7]	0.01
Previous suicidality	6.0 [2.4–14.8]	<0.001
Previous self-harm	2.0 [1.2–3.5]	0.01

Note: Logistic regression analysis. Method: Stepwise backward (Wald). All possible predictors were dichotomized. Here is shown the logistic regression model from the final step (step 3). Comorbidity and age were found not significant and were excluded stepwise from the model.

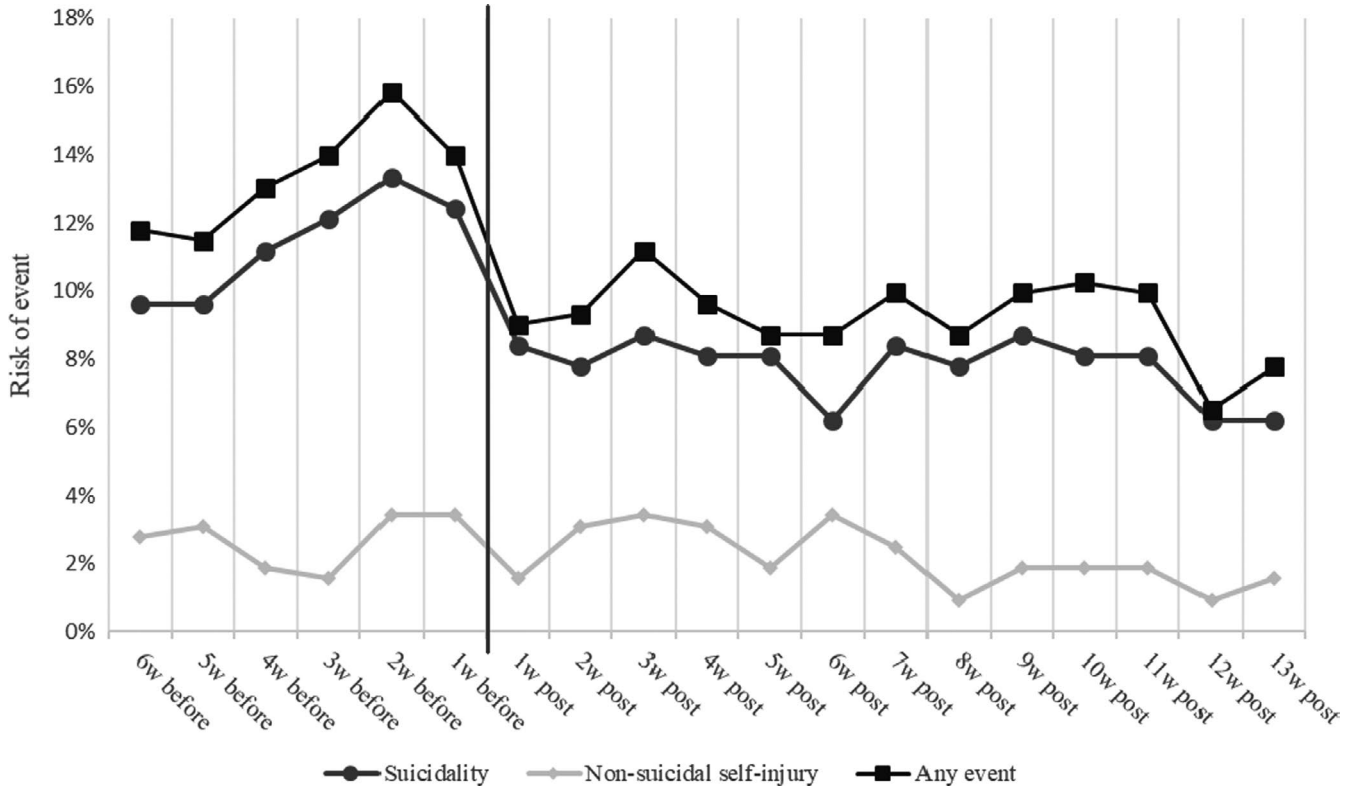

FIGURE 1 Time line for the risk of at least one event of suicidality, NSSI or any event (suicidality, NSSI or indeterminate) by week before and after SSRI initiation. The vertical line represents day of SSRI initiation. $N = 321$. NSSI, Non-suicidal self-injury

In the present study, the risk of suicide attempt, suicidal behaviour and suicidal ideation decreased after SSRI initiation. The majority of children and adolescents in the study had at least one event of suicidality in the study period before the initiation of SSRIs. Suicidal ideation was the most common suicidality event. The risk of suicidality decreased statistically significantly after SSRI initiation. Likewise, NSSI was frequently observed and decreased after the initiation of SSRIs. To investigate the immediate changes following SSRI initiation, the risk of suicidality was compared between the 6 weeks preceding and the 6 weeks following SSRI initiation. Like the findings from the standardized observation periods, the risk of suicidality decreased statistically significantly in the 6 weeks following SSRI initiation compared with the 6 weeks preceding. Unlike the results from the standardized observation periods, the decrease in NSSI in the 6-week period immediately following SSRI initiation was statistically non-significant.

The risk of suicidality after SSRI initiation in this study corresponds to the level found by Kuba et al.,[18] in which 22.9% of the patients had suicide-related events (suicidal ideation, self-mutilation and suicide attempt) during 3-month antidepressant therapy, but the risk of suicide attempt was low compared with the findings by Wilkinson et al., in which 17% of the patients made at least one suicide attempt in the month before baseline and 30% had at least one suicide attempt in the 28-week follow-up period. The patients in the Wilkinson et al. study were older (11–17 years) and all had major depressive disorder, which could explain the higher incidence of suicide attempts compared with this study. The risk of NSSI was lower compared with the Wilkinson et al. study in which 36% had at least one event of NSSI in the month before treatment and 37% had at least one event of NSSI in the follow-up period.[20]

In the present study, the majority of patients were treated with non-pharmacological interventions prior to and in parallel with SSRIs.[28] Patients who were not treated with non-pharmacological interventions in parallel with SSRIs were less likely to experience suicidality during SSRI treatment, but not in the 6-week period immediately following SSRI initiation. This finding might suggest that clinicians are more inclined to intervene, when patients exhibit suicidality. The level of non-pharmacological care prior to SSRI initiation did not influence the risk of suicidality. In the present study, inpatients were more likely to experience suicidality events than outpatients probably reflecting the severity of illness in this group of patients or that these patients are monitored more closely, why more events are detected.

Data on whether a patient stopped SSRI treatment during the observation period were not registered

according to protocol. Accordingly, when interpreting the results, it must be noted that a patient was considered exposed for the entire period even if they stopped SSRI treatment. The focus of the present study is the risk of suicidality associated with the initiation of SSRIs in a naturalistic setting. From previous studies, it appears that the risk of suicidality is increased during periods of titration and during discontinuation of antidepressants.[27] Furthermore, if suicidality occurred during SSRI treatment, discontinuation of treatment is a likely reaction. These issues complicate the disentanglement of the emergence of suicidality related to changes in SSRI treatment.

For the occurrence of events rather than individuals with events, the total number of suicidality events decreased in the 6 weeks following SSRI initiation compared with the 6 weeks preceding SSRI initiation. Interestingly, there was an increase in events of suicide attempts, but this finding did not reach statistical significance. NSSI events increased statistically non-significantly in the 6 weeks following SSRI initiation compared with the 6 weeks preceding SSRI initiation.

Suicidality within the first 6 weeks after SSRI initiation was predicted by previous suicidality, depression as indication for SSRIs, female gender and previous NSSI. Age and comorbidity did not predict suicidality in the regression model.

Previous suicide attempt is a well-known risk factor for future attempts[16] in line with previous suicidality being the strongest predictor for suicidality during antidepressant treatment in this study and consistent with findings from other studies of predictors of suicidality during SSRI treatment.[18–21]

Depression is a factor strongly associated with suicidality for children and adolescents.[14] Data from RCTs of SSRIs versus placebo may indicate that SSRI treatment increases the risk of suicidality in children and adolescents when the indication is major depressive disorder, but not on other indications.[22] However, critics argue that it is better to consider the overall effect, then determine whether evidence suggests effect modification. The evidence that SSRIs cause suicidality when given for depression raises the probability that SSRIs have similar effects when given for other indications.[23,33] In this study, patients with depression as indication for SSRIs had a higher risk of suicidality in the first 6 weeks after SSRI initiation compared with patients receiving SSRIs for OCD, anxiety disorders or other indications. Patients with depression or depressive symptoms are more frequently monitored for suicidality during SSRI treatment than patients receiving SSRIs on other indications[28] why suicidality in other diagnostic groups might be underestimated, thus lessening the predictive value of depression for the risk of suicidality during SSRI treatment.

NSSI has previously been described as an independent risk factor for suicide attempt.[20] Results from other studies contradict this finding[34] indicating that NSSI should be viewed as a clinical syndrome separate from suicidality and not as the first step in a continuum with more severe forms of suicidality.[35] This study supports that NSSI is a risk factor for suicidality and should be considered when assessing the risk of suicidality for children and adolescents during SSRI treatment.

Female gender was a predictor for suicidality during SSRI treatment in this study and replicates findings from Kuba et al.,[18] while in the Wilkinson et al. study, female gender was not an independent predictor of suicide attempt.[20] Females have a higher rate of suicide attempts than males unrelated to antidepressant treatment,[17] whereas suicide is more common in male children and adolescents.[17]

Age was not an independent predictor for suicidality when other risk factors were controlled. Suicide is rare in childhood and early adolescence and becomes more frequent with increasing age.[17] Kuba et al. found that age over 15 years increased the risk of suicide-related events during SSRI treatment.[18] The findings in this study are in line with the findings of Wilkinson et al though their sample was older (11–17 years) than the present sample.[20] Data from RCTs did not suggest that age modifies the SSRI-related risk of suicidality[6] though it has been hypothesized that children have a higher risk of suicidality during antidepressant treatment than adolescents based on statistically non-significant findings.[7]

Comorbidity was not an independent risk factor when other risk factors were controlled. Comorbidity in this study was defined as having more than one psychiatric diagnosis on initiation date. Literature indicates that the risk of suicidality (unrelated to antidepressants) increases with the number of comorbid diagnoses.[14]

In this study, the risk of suicidality was highest in the weeks leading up to SSRI initiation and then declined sharply. This pattern adds to the findings from Simon et al., who found that the risk of suicide attempt is highest in the month before starting treatment with antidepressants in adults as well as for children and adolescents, and then gradually declines over the next 6 months.[26] From these observations, we cannot conclude that SSRIs have a specifically protective effect against suicidality, since the same pattern in timing of suicide attempts applied for treatment with psychotherapy.[15] The findings seem to indicate that treatment is initiated when the risk of suicidality is at a peak. The immediate decline must be held against the time-course of the treatment response to SSRIs. Meta-analyses of SSRI responses over time found statistically significant benefits of SSRIs 2 weeks after the initiation of treatment in paediatric MDD,[36] OCD[37] and anxiety disorders.[38]

Additionally, clinicians usually start with low initial dose and increase gradually (Table 1). There are several possible explanations for the immediate decline: Because of the lack of a control group, it is unknown whether the decline is a placebo effect. If not, the decline may be an early effect of SSRIs independent from the chore effect significant 2 weeks after treatment initiation. Alternatively, the decline in suicidality is caused by other interventions offered in parallel with medication. In fact, the vast majority of the present sample received non-pharmacological interventions prior to and in parallel with medication,[28] although patients who did not receive psychosocial interventions in parallel with SSRIs had lower risk of suicidality. Finally, the decline could simply be explained by natural variations in the occurrence of suicidality; the peak observed 2 weeks before SSRI initiation is an extreme, why the subsequent decline follows naturally. The same time pattern did not apply for NSSI. No clear time pattern between NSSI and SSRI initiation was found.

Our findings are by large generalizable to the whole population of SSRI-treated children across indications, due to the Danish health authorities limiting prescriptions of any psychopharmacological drug to be handled by specialists in child- and adolescent psychiatry, that is general practitioners must refer children and adolescents in need for psychiatric drug treatment to the specialist treatment. The majority of these specialists are affiliated with the hospital CAMHS clinics. In 2016, 65.7% of first prescriptions for antidepressants for children and adolescents were prescribed by doctors affiliated with hospital clinics, and 80.9% of children and adolescents with a psychiatric diagnosis had at least one hospital contact in 2016.[39] The CAMHS in Copenhagen is the largest in the country and all other CAMHS have similar diagnostic patient distributions and follow the same national guidelines.

The main limitation of the present study is the lack of a control group. The decreased risk of suicidality after SSRI initiation must be interpreted with caution in absence of a control group, because other factors than a pharmacological effect may have influenced the risk of suicidality and NSSI in our sample, including regression towards the mean. Compared with children and adolescents in the trials from meta-analyses, the children in this study had a higher level of pre-SSRI suicidality, more comorbidities and were treated with other pharmacological and non-pharmacological interventions prior to and in parallel with SSRIs. These factors influence the risk of suicidality and NSSI. On the other hand, because of these factors, the present sample might represent the average child and adolescent patient receiving SSRIs more truly than patients from drug trials. Another study limitation is the risk of detection bias. Guidelines recommend routine monitoring for suicidality after SSRI initiation,[24,32] why the occurrence of suicidality events before SSRI initiation might be underestimated, because of less monitoring for suicidality in the period before treatment versus after SSRI initiation. This detection bias may impact the results of the study: if the suicidality risk before SSRI initiation has been underestimated, the observed decrease in suicidality after SSRI initiation could be even higher than observed in the present study. In the present study, data were collected by two researchers. Interrater reliability of classification of suicidality and NSSI was not assessed which may cause inaccuracies. To limit this bias, questions of doubt were conferred with a specialist in child and adolescent psychiatry.

In conclusion, suicidality was common in 365 children and adolescents aged 7–18 years treated with SSRIs in child and mental health services. The risk of overall suicidality decreased, and attempted suicide was stable in the weeks following SSRI initiation. Previous suicidality, depression, female gender and previous NSSI are important predictors for suicidality during SSRI treatment.

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CONFLICT OF INTEREST

The authors state that they have no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical reasons.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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