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Comparing episodes of antidepressants use with intermittent episodes of no use: A higher relative risk of suicide attempts but not of suicide at young age

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Abstract

The Food and Drug Administration has issued a number of advisories regarding a possible causal link between antidepressants and suicide behaviour among young persons. We investigated the age dependency of (fatal) suicide attempts associated with antidepressants (N=232,561). By linking insurance claims with the death register of Statistics Netherlands (2002–2011), rates of (fatal) suicide attempts were estimated during antidepressant use and intermittent episodes without use. The age dependency of the relative risk of attempts and of suicide during episodes with compared with episodes without antidepressants was investigated by testing the {age × episode} interaction.

The attempt rate during antidepressant use decreased with increasing age, concurrently with a decrease of the relative risk from 3.62 to 1.86 (p for interaction <0.001). This age dependency was found both at the early (<0.5 year) and at later stages after the first prescription (>5 years). No suicides were found among those aged <18 years, and no age dependency for the relative risk of suicide at ages ⩾ 18 was established (p>0.46). The association between antidepressants and suicide attempts at a young age does not necessarily point to a causal relationship, and, most importantly, did not translate to a similar age dependency for suicide.

Keywords

Antidepressants, suicide, suicide attempts, age, pharmaco-epidemiology

Introduction

Since the 1990s, concerns have been raised about a possible causal relationship between use of antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs), and suicidal behaviour, in particular among the young (Donovan et al., 1999; Gibbons et al., 2007; Hammad et al., 2006). These concerns have resulted in a public health advisory issued by the Food and Drug Administration (FDA) in 2003 and in a 'black box warning' (McCain, 2009). In 2007, the warning was extended to young adults aged 18–25 years (Stone et al., 2009). However, ecological studies suggesting the reverse, also on suicide (Gibbons et al., 2007; Gusmao et al., 2013; Lu et al., 2014), leave psychiatrists and other health care providers in a cloud of uncertainty regarding the safety of antidepressants.

Results of various randomized controlled trials (RTCs) (Stone et al., 2009) and some observational studies with individual level data have shown that antidepressants may be associated with increased risk of suicide (attempts) among the young (Martinez et al., 2005; Miller et al., 2014; Olfson et al., 2006; Tiihonen et al., 2006). An age-dependent risk of suicide behaviour associated with use of antidepressants was found in the meta-analysis of placebo-controlled clinical trials (Stone et al., 2009). These findings were mainly based on adverse event reports, which may be sensitive to ascertainment bias (Gibbons et al., 2007). Furthermore, the numbers of registered fatal suicide attempts in the trials on which the FDA advisories were based were very small (N=8 in the adult, none in the paediatric studies) and were related to the early treatment phases only (Gibbons et al., 2007). In the observational studies, on the other hand, the higher risk may be explained by the underlying disorder and not necessarily by a causal effect of antidepressants. In the well-designed propensity-score matched study using health care utilization data among 162,625 US residents with depression, a prescribed high dose of SSRI was significantly associated with a higher rate of deliberate self-harm (hazard ratio=2.2) among those aged <25

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years, but equal rates were found among those aged ⩾25 (Miller et al., 2014). This finding suggests the presence of an adverse effect of antidepressants specifically associated with young age, but confounding by indication may (partly) explain these results and, most important, the relevance of self-harm for risk of suicide (attempts) remains a question (Barbui and Patten, 2014).

In a recent study with health insurance data in the Netherlands, we found higher rates of suicide attempts and a slower decrease in these rates during episodes of antidepressant use in the first months directly following antidepressant initiation among those aged <25 years compared with those aged ⩾25 years. However, a higher rate of attempts among the young was already found during the month prior to initiation. These results strongly suggest that at young age predominantly those with more severe symptoms start with antidepressants, and effectiveness of antidepressants to prevent suicide behaviour is lower in young patients compared with older patients (Termorshuizen et al., 2015). Remarkably, no similar age dependency was found for suicide, with the highest rates shortly after the start among those aged ⩾40 years.

As the previous study (Termorshuizen et al., 2015) focused on the early treatment phases, the number of suicides was small. The aim of the present study (using the same database) was to investigate the age dependency of both risk of suicide attempt and of suicide during episodes of antidepressant use. It was hypothesized that the unfavourable age dependency of attempt risk during episodes of antidepressant use may also be established over extended periods of the treatment trajectory and may translate into a similar age dependency for suicide risk.

Method

Databases

In this cohort study, the first data source was the Achmea Health Insurance Database (AHD). Achmea is one of the largest health insurance companies in the Netherlands with policyholders spread over the country but with the centre of the Netherlands as one of the dominant regions. Although it is a private company, insurance for the provision of medical care is compulsory for all inhabitants in the Netherlands, and, thus, the data from the Achmea Health Database may be regarded as reasonably representative for the health care utilization of the Dutch population. In the AHD, all reimbursements for the provision of medical care to the insured patients of insurance company Achmea are recorded. This includes drug prescriptions delivered by pharmacists and so called Diagnostic Treatment Protocols (in Dutch: 'Diagnose Behandel Combinatie' (DBC)). A DBC is an insurance claim containing codes for diagnosis and treatment by a medical specialist. The second data source is the population register and the linked death register of Statistics Netherlands (in Dutch: Centraal Bureau voor de Statistiek (CBS)). The CBS is responsible for collecting individual and population data in the Netherlands. Physicians in the Netherlands are obliged to report the cause of death to the civil registry of the town where the person died. This is forwarded to the CBS, where the death report is ICD-10 coded. Dutch privacy law allows use of administrative data sources for scientific research under strict conditions in relation to anonymity and storage, in which case informed consent of the patients is not needed.

Patients and data-extraction

From the AHD, all patients with at least one registered prescription for antidepressant in the period January 2001–March 2013 were selected, regardless of the prescriber (general practitioner, psychiatrist or other specialist). By using the civil number, the records of these patients were linked to the population register, resulting in a match of nearly 100%. For the matched patients (*N*=322,435), all prescriptions following the date of the first dispensed antidepressant ('index date') were used to define episodes of antidepressant use and episodes of no antidepressant use thereafter. Antidepressants were prescriptions with Anatomic Therapeutic Chemical codes N06AB (SSRIs), N06AA (tricyclic antidepressants (TCAs)) and all other codes in the N06A category (other). The duration of a prescription was assessed by dividing the cumulative number of defined daily dosages (DDDs) by the prescribed daily dosage (PDD). Patients with at least one prescription with conflicting data on DDD and/or PDD that could not be easily corrected were excluded from further analyses (*N*=276,655 remaining). Two weeks were added to the calculated duration of each prescription to take into account forgotten medication that might be caught up later and a wash-out period after finishing (half-time of antidepressants is often only one day (e.g. paroxetine) or a few days (e.g. escitalopram), sometimes longer, 1–2 weeks (e.g. fluoxetine) (Preskorn, 1997)). If within these two weeks or earlier a new prescription for the same class of antidepressants was dispensed, the defined episode of use was continued. If the lag time between the end date of the last prescription (plus the two-week window) and the start date of the next prescription was longer, an episode of no antidepressant use until restart was defined. If a prescription of an antidepressant from another category was dispensed, a new episode of antidepressant use was defined starting at the date of dispensing and the earlier episode was regarded as finished. After the last defined episode of use, the start of an episode of no use was defined. This episode lasted until the last date of actual insurance or to 31 December 2011, whichever of these dates came earlier. The selection for the analysis was further restricted to those patients with at least one year of insurance without antidepressant use prior to the index date (*N*=245,067). As the follow-up was restricted to the years 2002–2011 to take possible delay in reporting into account, the study group was restricted to those who started their first registered antidepressant use before 1 January 2012 (*N*=232,561) (see the Online Appendix).

In a next step, the data were linked to the causes of death register for the years 2002–2011 to find suicide events following the index date. The ICD-10 codes X60-84 (intentional self-harm) and Y10-34 (event of undetermined intent) were regarded as suicides. Also, the registered treatments with a DBC code for psychiatric consultation in hospital (code for specialism 0329) in combination with a code for suicide attempt (code for care demand 01), or with a code for internal medicine (code 0313) in combination with a diagnosis of (auto-)intoxication (code for diagnosis 042) were extracted from the AHD. These codes were regarded as indicative of a suicide attempt. DBC codes 0329/01 point with high probability to the presence of a suicide attempt. It is the psychiatrist who evaluates and registers the attempt. DBC codes 0313/042 point with less certainty to the presence of an attempt (see Discussion), which necessitates a sensitivity analysis excluding these codes from the definition of attempt. This

code always indicates that poisoning was the method in the case of a suicide attempt and this is evaluated by the specialist/internist according to his/her clinical insight, the details of which are not part of the insurance claim. Suicides and suicide attempts were assigned to the episode of antidepressant use or (intermittent) episode of no use during which they occurred. In the case of a suicide attempt, the episode was truncated at the date of this attempt and was restarted as a new episode thereafter.

Outcomes

In the first analysis, suicide attempt was the outcome of interest. As the DBC registration became operational from January 2006 onwards, episodes that were finished before January 2006 were excluded. Episodes that started before January 2006, but ended thereafter were redefined with a new start date at 1 January 2006. This restricted the sample available for this analysis (N=183,725 patients). In the second analysis, suicide was the primary outcome (N=232,561 patients).

Analysis of suicide attempts

Crude rates of suicide attempts (number/10,000 person-years) were calculated for episodes of antidepressant use and for (intermittent) episodes of no use, and for different age categories (<18, 18–24, 25–39, 40–60, and ⩾60 years) separately. A Poisson model was applied to estimate the Incidence rate ratio (IRR) of suicide attempts during episodes of antidepressant use compared with episodes of no use.

In a Poisson model, the outcome variable is the number of events per observation time. The Poisson model makes it possible to handle multiple events within the same person by inclusion of a random intercept (see below). It was tested whether there were differences in this IRR between age categories by inclusion of terms for {age × episode} interaction. Furthermore it was examined whether these differences were still present after adjustment for gender, ethnic origin, duration since the index (<0.5, 0.5–2, 2–5, > 5 years) and presence of a DBC indicative of specialist mental health care, and after taking into account age-specific differences in patterns of antidepressant use. Dependence between episodes within the same patient was taken into account by inclusion of a random intercept. In a next step, it was examined whether duration since index date modified the (possible) {age × episode} interaction. This was done by inclusion of terms for second-order interaction between duration and {age × episode}. The model-specific standard errors were used to estimate the 95% confidence intervals (CIs).

Analysis of suicides

Crude rates of suicides (number/10,000 person-years) were calculated in a similar way. The interaction of {age × episode} was tested in a Cox model. In a Cox model, the outcome variable is the duration until the event of interest ('survival time'), after which the follow-up of that individual is finished. The survival time started at the date of the first registered prescription of antidepressant (the index date) and ended at the end date of the last registered episode or death. 'Episode', indicating current antidepressant use or no use, was included as a time-dependent variable.

Data-management, record linking, description of the study cohort and estimation of crude suicide (attempt) rates were performed using SPSS, version 14.0. The Cox and random-intercept Poisson regression analyses were performed using STATA, version 11.0 (Cleves et al., 2004; Rabe-Hesketh and Skrondal, 2005).

Results

Description

Patients' and treatment characteristics are given in Table 1. Among the included patients, 978,430 episodes of use and 855,316 episodes of no use were defined. For the analysis on suicide attempts, the data of 183,725 patients and of 487,436 episodes of use were available. The distribution of age, gender, ethnic origin and nature of antidepressant episodes were roughly similar for this selection of patients (data available on request).

Use of antidepressant and age

Among those aged <18 years and 18–<25 years, the majority of time of antidepressant use was associated with SSRI use (71.3% and 70.8%) (Table 2). At higher ages, this percentage became less in favour of use of TCAs and other antidepressants. The percentage of antidepressant users with more than 10 registered antidepressant prescriptions increased from 24.8% among those aged <18 to 38.6% among those aged ⩾60. Thus, at older age the percentage of chronic antidepressant users appears to be higher. In accordance with this notion, the percentage observation time associated with episodes of no use which were not followed by a registered restart declined from 73.7% among those aged <18 years to 46.6% among those ⩾60 years. These differences in prescription pattern necessitate a number of sensitivity analyses (see below).

Analysis of suicide attempts

In Table 3, the number of suicide attempts during episodes of use and (intermittent) episodes of no use are given for the different age categories. High rates were found at young age and a trend to lower rates at older age. As the absolute number of suicide attempts was small among those aged <18 years and no large difference in suicide attempt rates with those aged 18–<25 years were found, these age categories were collapsed for the Poisson analysis.

The IRR of suicide attempts for episodes of antidepressant use compared with episodes of no use decreased from 3.62 among those aged <25 years to 1.86 among those aged ⩾60 years (Table 3, last column). The terms for the interaction {age × episode} were statistically significant (p<0.001). Similar results were found when restricting the analysis to a minority of participants with a known diagnosis of a depressive disorder (11.1%, from available DBCs, not necessarily the diagnosis at the time of first prescribed antidepressant): the IRR decreased from 3.06 (2.24–4.16) for those aged <25 to 1.20 (0.81–1.76) for those aged ⩾60 years.

The high IRR associated with the young age category became somewhat less pronounced when restricting the analysis to episodes of SSRI use and to those with at least one episode of SSRI use (IRR=2.94), but the {age × episode} interaction was still

Table 1. Description study cohort 2002–2011.

Age at the start of first episode, years, mean (SD)	49.4 (18.3)	
Age at the start of first episode, years, categories		
<18	2970 1.3%	
18–< 25	13,246 5.7%	
25–<40	65,700 28.3%	
40–<60	86,146 37.0%	
⩾60	64,499 27.7%	
Gender male	83,016 35.7%	
Ethnic origin non-Dutch	74,250 31.9%	
Nature of eps of use per unique patient (number of patients/number of eps of AD use)		
1. Only eps with SSRI	96,675/361,245	41.6/36.9%
2. Only eps with TCA	52,925/144,660	22.8/14.7%
3. Only eps with other AD	30,246/82,090	13.0/8.3%
4. Only eps with combination of ADs	107/150	0.0/0.0%
5. Eps with SSRI and eps with TCA	13,234/80,630	5.7/8.2%
6. Eps with SSRI and eps with other AD	20,381/128,976	8.8/13.1%
7. Eps with TCA and eps with other AD	5895/32,313	2.5/3.3%
8. Eps with SSRI and eps with TCA and eps with other AD	6758/63,431	2.9/6.4%
9. All other combinations of eps	6340/84,935	2.7/8.6%
Total number of patients/	232,561/	100/100%
number of episodes of use/	978,430/	
episodes without use of ADs	855,316	

eps: episodes; AD: antidepressant; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

Table 2. Description of use of antidepressants by age category (2002–2011).

Age, years	<18	18–<25	25–<40	40–<60	60⩾
Percentage of time during episodes of AD use associated with:					
SSRI	71.3%	70.8	66.9	59.5	53.0
TCA	18.7%	9.5	11.4	18.8	27.7
Other AD/combination of ADs	10.0%	19.8	21.7	21.7	19.3
Number of AD prescriptions during observation time, % 1	23.9%	19.9	15.7	16.8	21.7
1–10	51.3%	47.5	43.2	39.5	39.7
>10	24.8%	32.7	41.1	43.7	38.6
Percentage of time during the observation period associated with:					
Use of ADs	15.1%	19.4	26.6	33.9	36.5
No use of ADs – intermittent	11.1%	19.6	21.6	19.9	16.7
No use of ADs – not followed by new episode of use of AD	73.7%	60.9	51.7	46.0	46.6

AD: antidepressant; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

significant ($p<0.001$) with a vanishing IRR at age ⩾60 years (IRR=1.20, 95% CI: 0.83–1.74).

Similar results were found when excluding children younger than 12 years of age, and/or when restricting the analysis to those with at least two prescriptions for antidepressant, and/or when using only the DBC codes for psychiatric consultation in hospital for definition of a suicide attempt (data not shown). Furthermore, similar results were found when truncating the last episode of no use at six months or at three months if it was not followed by a registered restart (data not shown). After adjustment for gender, ethnic origin, duration since the index and presence of a DBC for mental health care, the high IRRs associated with the younger age categories became somewhat less pronounced (IRRs=2.48 and 2.20, respectively), but the {age × episode} interaction was still significant ($p<0.001$).

The higher IRR of attempts at young age was found within all strata for the duration since the first prescribed antidepressant (<0.5, 0.5–2, 2–5, ⩾5 years) (p value for second order

Table 3. Crude suicide rates by episodes of use of antidepressants versus episodes of no use, stratified by age at the start of an episode. Poisson regression on suicide attempts (last column): bivariable model with age, episodes of antidepressant use versus no use, and interaction (I×) of {age × episode}.

	Number of persons	Number of episodes	Follow-up time, years	Number of suicide attempts DBC 0329-1101/ DBC 0313-042	Suicide attempt rate DBC 0329-1101/ DBC 0313-042, number/10,000 person-years (95% CI)	Poisson model IRR associated with episodes of use compared with episodes of no use (95% CI)
<18 years of age						
Episodes of use with AD	1329	2254	718.9	8/9	236.4 (137.7–378.6)	
Episodes of no use	1587	2335	4907.2	12/20	65.2 (44.6–92.0)	
18 –<25 years of age						
Episodes of use with AD	6831	14,590	4408.9	32/95	288.0 (240.1– 342.7)	3.62 (2.84–4.62)[a]
Episodes of no use	7834	14,363	21,044.8	27/154	86.0 (73.9–99.4)	1.00
25–<40 years of age						
Episodes of use with AD	34,071	107,355	37,112.3	123/337	123.9 (112.8–135.8)	3.16 (2.74–3.66)
Episodes of no use	44,436	109,196	142,619.1	107/427	37.4 (34.3–40.7)	1.00
40–<60 years of age						
Episodes of use with AD	59,167	222,327	90,161.7	138/492	69.8 (64.5–75.5)	2.32 (2.04–2.63)
Episodes of no use	74,243	216,203	231,302.7	179/462	27.7 (25.6–29.9)	1.00
⩾60 years of age						
Episodes of use with AD	46,470	140,910	67,718.4	39/105	21.2 (17.9–25.0)	1.86 (1.47–2.37)
Episodes of no use	56,258	136,474	154,867.4	53/120	11.1 (9.5–12.9)	1.00
Total						I× {age-categorized × episode}: p<0.001 (df=3)
Episodes of use with AD	183,725	487,436	200,120.3	340/1038	68.8 (65.2–72.5)	I× {age-continuous × episode}: p<0.001 (df=1)
Episodes of no use	173,494	478,571	554,741.4	378/1183	28.1 (26.7–29.5)	

[a] The age categories <18 and 18–<25 years were collapsed into one category for the Poisson analysis.
DBC: Diagnose Behandel Combinatie [Diagnostic Treatment Protocols]; CI: confidence interval; IRR: incidence rate ratio; AD: antidepressant.

interaction of {duration × {age × episode}} =0.6852, df=12). The IRR for those aged <25 years was even slightly higher for the strata of 2–5 and >5 years (IRR=3.47 and IRR=3.42) than for the strata of <0.5 and 0.5–2 years (IRR=2.51 and IRR=2.41) (data not shown).

Analysis of suicides

In Table 4, the crude suicide rates are shown by age category. No suicide events were registered for patients younger than 18 years. This age category was excluded from the Cox analysis. At ages ⩾18 years, episodes of antidepressant use were associated with considerably higher rates of suicide compared with episodes of no antidepressant use. With increasing age there was a trend to increasing suicide rates, both during episodes of use and during episodes of no use. In the bivariable Cox regression analysis, the hazard ratio of suicide during episodes of antidepressant use compared with episodes of no use decreased slightly with increasing age (Table 4, last column). The terms for the interaction of {age × episode}, however, were far from statistically significant (p>0.46). Similar results were found when excluding suicide events with the codes Y10-34 (events of undetermined intent) from the analysis (n=26). A similar picture was found when restricting the analysis to episodes of SSRI use: no significant interaction of {age × episode} (p>0.70) and a significantly increased hazard ratio at ages ⩾60 years (hazard ratio=1.55, 95% CI: 1.01–2.38). The last finding contrasted with the vanishing IRR of attempts among SSRI users at high age (see above).

Furthermore, similar results were found after adjustment (see above), or when restricting the data to those with at least two prescriptions for antidepressant or when truncating the last episode of no use at six months if it was not followed by a restart (data not shown).

Discussion

We found high rates of suicide attempts during antidepressant use among those aged <25 years, and the IRR of attempts during episodes of use compared with episodes of no use was statistically significantly higher among the young than among those at higher age. This age dependency was also found in patients with long-term history of antidepressant use (first registered antidepressant prescription >5 years ago). We found no registered suicides among antidepressant users aged <18 years, a trend towards higher suicide rates with increasing age, and no significant age dependency in the hazard ratio of suicide death in the age categories ⩾18 years. Thus, these results show an unfavourable association between antidepressants and suicide attempts especially at young age, as was also found for the early phases directly following the start of medication (Termorshuizen et al., 2015). These results also show that the increased relative risk of suicide attempts at an early age does not translate to a similar age dependency for suicide risk.

Table 4. Crude suicide attempt rates by episodes of use of antidepressants versus episodes of no use, stratified by age at the start of an episode. Cox regression on suicides (last column): bivariable model with age, episodes of antidepressant use versus no use, and interaction (I×) of {age × episode}.

	Number of persons	Number of episodes	Follow-up time, years	Number of suicides	Suicide rate, number/10,000 person-years (95% CI)	Cox model Hazard ratio associated with episodes of use compared with episodes of no use (95% CI)
<18 years of age						
Episodes of use with AD	2970	5348	1608.1	0	0.0	
Episodes of no use	2521	4508	8830.5	0	0.0	
18–<25 years of age						
Episodes of use with AD	13,864	31,033	9624.3	5	5.2 (1.6–12.1)	2.70 (0.77–9.36)[a]
Episodes of no use	12,546	26,681	38,366.8	5	1.3 (0.4–3.0)	1.00
25–<40 years of age						
Episodes of use with AD	69,386	242,704	85,972.7	66	7.6 (5.9–9.7)	2.23 (1.56–3.18)
Episodes of no use	64,885	212,568	228,720.1	61	2.6 (2.0–3.4)	1.00
40–<60 years of age						
Episodes of use with AD	98,822	431,925	173,532.9	165	9.5 (8.1–11.0)	2.21 (1.74–2.82)
Episodes of no use	94,224	380,162	327,896.7	119	3.6 (3.0–4.3)	1.00
⩾60 years of age						
Episodes of use with AD	72,860	267,420	120,069.1	96	8.0 (6.4–9.7)	1.97 (1.44–2.68)
Episodes of no use	67,168	231,397	206,889.0	73	3.5 (2.7–4.4)	1.00
Total						I× {age-categorized × episode}: p=0.9063 (df=3)
Episodes of use with AD	232,561	978,430	390,807.2	332	8.5 (7.6–9.4)	I× {age-continuous × episode}: p=0.4664 (df=1)
Episodes of no use	218,036	855,316	810,703.3	258	3.1 (2.8–3.6)	

[a] The age category <18 years was excluded from the Cox analysis.
CI: confidence interval; AD: antidepressant.

Comparison with other studies

If a causal relationship between antidepressants and suicide behaviour, especially at young age, is present, this is probably restricted to the early stages following the initiation of treatment (Morrison and Schwartz, 2014). Several studies show that, indeed, the risk of suicide attempts is high shortly after the start of antidepressant use (Jick et al., 2004; Termorshuizen et al., 2015; Valuck et al., 2004). However, these findings may reflect the severity of the mental disorder in the early phases when antidepressants have not yet exerted their beneficial effects. In our earlier study, we found much higher pre-treatment levels of suicide attempts among the young than among the elderly (Termorshuizen et al., 2015). The present study contributes to these findings by showing that the unfavourable association between antidepressant use and suicide attempts at a young age is not restricted to the early phases after the first antidepressant prescription. This finding is not consistent with the presence of a causal relationship between antidepressants and suicide attempts but instead suggests confounding by indication as explanation.

Prospectively measuring suicidal thoughts and behaviour by means of standardized rating scales such as were used in a recent re-analysis of randomized placebo-controlled trials of fluoxetine and venlafaxine may give a valid picture of suicide behaviour during use of antidepressants (Gibbons et al., 2012). This analysis did not show an unfavourable effect of treatment with antidepressants on suicide ideation/attempts among the young. However, a favourable treatment response with reduction of depressive symptoms was also not associated with a concomitant reduction of suicide behaviour risk, contrary to expectation. This contrasted with the findings among adults. These results suggest that treatment with antidepressants does not pave the way for suicide behaviour, but that antidepressants may be less effective in preventing this at young age. The lower effectiveness at young age may also explain the age dependency in the IRR of suicide attempts observed in the present study. This lower effectiveness may also be explained by lower adherence to treatment at young age or by a higher risk of treatment resistance associated with more severe clinical symptoms among younger patients before getting antidepressants prescribed.

In the study by Simon et al., in which health insurance data of 65,103 health plan members diagnosed with a depressive disorder and with at least one episode of prescribed antidepressant during 1992–2003 were analysed, a substantial reduction in suicide attempt risk after treatment initiation was not associated with a similar reduction in suicide risk (Simon et al., 2006). In the cohort study by Tiihonen et al. among 15,390 high-risk patients in Finland with a previous suicide attempt, using a nationwide computerized database on hospital admissions and medication prescriptions, current antidepressant use was associated with a significantly increased risk of suicide attempts, but not of suicide (Tiihonen et al., 2006). These studies show that suicide attempts and suicides are distinct phenomena (Fergusson et al., 2005) and are in accordance with the diverging patterns for suicide attempts and suicide death found in the current and in our earlier study (Termorshuizen et al., 2015).

Strengths and limitations

Patients often switch from one antidepressant to another or stop temporarily, and, thus, the comparison of episodes of use with episodes of no use is relevant for the treatment trajectories over extended periods of time. Analyses of large administrative databases like the present study are important to assess the risk of suicide during antidepressant use, as the number of registered fatal suicide attempts in the trials underlying the FDA warnings included only a very few cases (N=8 in the adult, none in the paediatric studies) (Stone et al., 2009). Differences in prescription patterns of antidepressant across age categories were taken into account by performing a number of sensitivity analyses. By truncating long episodes of no use and by excluding patients with only one prescription, we explored whether the effects of episode and the interaction with age were due to possible overrepresentation of those with lower tendency towards suicide behaviour in the observation time during episodes of no use.

An important limitation is that diagnoses related to prescription of antidepressants were not taken into account. Differences in diagnoses and severity may explain the differences found between the age categories. Even if the age dependency for suicide attempts is fully explained by confounding by indication, the more remarkable and stronger is the finding of no parallel age dependency for suicide as cause of death.

A number of suicide attempts has probably been missed as only a part of the attempts (about one-third) get medical attention and are followed by treatment (Eaton et al., 2012). In addition, a number of as such defined attempts in our study may have been misclassified, especially those that were related to a DBC code for diagnosis of (auto-)intoxication. Still, poisoning by toxic substances is the most common method of suicide attempt leading to hospital admission and may be regarded as a valid indicator of suicide attempts in population-based studies (Lu et al., 2014; Patrick et al., 2010). Furthermore, similar results were found when restricting the analysis for attempts to the appropriate DBC codes for psychiatric consultation. Establishment of suicide attempts using administrative data is prone to underestimation and misclassification and this introduces a source of uncertainty. Even if a lower level of underestimation at young age is present, this does not yet explain the observed age dependency in the contrast of suicide attempt risk between episodes of use versus episodes of no use.

Another limitation is that our study was restricted to one country, the Netherlands. Various studies show that differences in the distributions of symptoms and associated suicide risk within the spectrum of depressive disorders across countries are present (Jeon et al. 2013, 2014), for example, the higher prevalence of melancholic features and lower experience of depressed mood among Korean patients compared with American patients with Major Depressive Disorder may be associated with poorer treatment response and/or selection of patients at more advanced stages of their disease, which may lead to a higher risk of suicide behaviour during use of antidepressants (Jeon et al., 2014). Studies into cross-cultural differences are needed to evaluate the influence of psychopharmacological treatment on suicide behaviour in different populations.

In conclusion, an experimental placebo-controlled study with an enormous number of participants over a broad age range and with well-designed longitudinal data collection would be needed to settle the debate on the existence of a causal link between antidepressants and suicide (attempts) definitely. As ethical and practical considerations preclude the implementation of such a trial, additional data from observational studies are important (Meyer et al., 2010). The present study contributes to earlier RCTs and observational studies by confirming that young patients using antidepressants are of particular concern. The higher risk of attempts at young age, however, is not necessarily caused by antidepressants and, most importantly, is not accompanied by a similar risk of suicide.

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