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To Be Continued? Long-Term Treatment Effects of Antidepressant Drug Classes and Individual Antidepressants on the Risk of Developing Dementia:

A German Case-Control Study

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ABSTRACT

Background: Given the need for disease-modifying therapies for dementia, drug repurposing appears to be a promising approach, at least as a risk reduction treatment. Preclinical studies suggest that antidepressants—in particular selective serotonin reuptake inhibitors—have beneficial effects on dementia-related biomarkers and functional outcomes, although clinical data are inconclusive. The present case-control study aimed to evaluate the effects of antidepressant drug classes and individual compounds with different treatment durations on the risk of developing dementia.

Methods: Analyses are based on data from the German Disease Analyzer database (owned and maintained by IQVIA) and included 62,317 subjects with an incident dementia diagnosis (*ICD-10*: F01, F03, G30, F06.7) and controls matched by age, sex, and physician between January 2013 and December 2017. Logistic regression analyses adjusting for health insurance status and comorbid diseases associated with dementia or antidepressant use were performed to investigate the association between dementia incidence and treatment with 4 major antidepressant drug classes and 14 of the most frequently prescribed individual substances.

Results: In 17 of 18 comparisons, long-term treatment (≥ 2 years) with any antidepressant was associated with a lower incidence of dementia than short-term treatment. Tricyclic and herbal antidepressants were associated with a decrease in dementia incidence, especially with long-term treatment. The lowest risks for dementia on an individual substance basis were identified for long-term treatment with escitalopram (odds ratio [OR] = 0.66; 95% CI, 0.50–0.89) and *Hypericum perforatum* (OR = 0.6; 95% CI, 0.51–0.70).

Conclusions: Long-term treatment with tricyclic antidepressants, *Hypericum perforatum*, or escitalopram may be associated with reduced incidence of dementia. If antidepressant therapy is well tolerated, continuation—even if depressive symptoms have resolved—may be considered even beyond the purpose of relapse prevention. Future combined analyses of multinational registries and long-term clinical trials are needed to substantiate these findings.

J Clin Psychiatry 2020;81(5):19m13205

To cite: Bartels C, Belz M, Vogelgsang J, et al. To be continued? Long-term treatment effects of antidepressant drug classes and individual antidepressants on the risk of developing dementia: a German case-control study. *J Clin Psychiatry*. 2020;81(5):19m13205.

To share: https://doi.org/10.4088/JCP.19m13205

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Driven primarily by demographic change, the prevalence of dementia is steadily increasing,[1] causing an urgent need for the development of effective disease-modifying, preventive, or risk-reduction treatments. For Alzheimer's disease (AD), the most frequent cause of dementia, available symptomatic medication is approved only for conditions of dementia in which patients already suffer from severe cognitive decline. Since molecular pathophysiology in AD already occurs years to decades before first clinical symptoms arise,[2] more recent approaches have focused on earlier stages of AD and preventive strategies.[3] Mild cognitive impairment (MCI) is a pre-dementia stage in which pathologic features of AD can already be detected by biomarkers.[4] Overall, a treatment that delays dementia onset would reduce dementia prevalence noticeably.[3] In particular, interventions addressing modifiable dementia risk factors may have considerable impact in terms of risk reduction, prevention, or delayed progression. To accelerate accessibility, repurposing already approved medication for additional indications has been recognized as a promising strategy.[5]

Depression could represent one of these potentially modifiable risk factors for all-cause dementia.[3] Numerous studies[6–10] have concordantly demonstrated a strong association between depression and an increased risk of subsequent dementia. Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depressive symptoms in AD dementia. Preclinical research in recent years has suggested that SSRIs reduce amyloid plaque burden in transgenic mouse models of AD and in cognitively healthy humans,[11–13] attenuate amyloid-β_{1-42}–induced tau hyperphosphorylation in cell culture,[14] and improve cognition in mice.[13,15]

However, randomized clinical trials testing effects of SSRIs on cognition in AD dementia have mostly yielded negative results.[16–22] As the

Clinical Points

- Depression is a potentially modifiable risk factor for dementia, but effects of antidepressants—both drug classes and individual substances—and treatment duration on the progression to dementia are unclear so far.
- If due caution is observed, continuation of antidepressant therapy even beyond remission of depression may be considered in old-age depression and may be associated with a reduced risk of developing dementia.

only exceptions, 1 clinical trial[23] with 12-week sertraline treatment found favorable effects, and the only study[24] with MCI subjects showed positive results on cognition with fluoxetine treatment.

In addition to clinical trials, a growing body of evidence has accumulated using registries and epidemiologic databases. When investigating the general impact of antidepressants on cognitive decline or dementia, these studies found either no association,[25,26] a 2-fold risk increase,[27] or a lower mortality risk.[28] To test for effects of differential treatments, various antidepressants were grouped into drug classes, and—in most cases—subjects without antidepressant medication were compared to those with SSRI or tricyclic antidepressant (TCA) use. Thus, controversial findings have been collected with (1) both SSRIs and TCAs increasing the risk of MCI or dementia,[29–32] (2) both exerting no effect on dementia risk,[33] or (3) mixed results favoring TCA use,[34,35] with an increased dementia risk with SSRIs[36] or outcomes favoring SSRI use.[37–39]

Few studies have addressed which antidepressants may influence the risk of developing dementia. Burke et al[40] reported that individual antidepressants (mainly SSRIs) reversed the increased dementia risk to a nonsignificant level, with the lowest hazard ratios for escitalopram. In a recent study[41]—with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) but without TCAs—only venlafaxine significantly decreased dementia risk.

Furthermore, evidence for treatment duration effects on the risk of developing dementia is particularly rare. Data from Danish registries suggest that long-term antidepressant treatment decreases the overall dementia rate,[42] mainly attributable to protective effects of TCAs, whereas no effects could be found for SSRIs or newer non-SSRIs.[43] In contrast, Bartels et al[44] were able to demonstrate that long-term SSRI treatment (> 4 years) could delay clinical progression from MCI to AD dementia in patients with a history of depression by 3 years.

On the basis of these promising effects of long-term SSRI treatment, we aimed to analyze the effects of different antidepressants on the risk of developing dementia in a case-control study. Specifically, we investigated the effects of (1) 4 major antidepressant drug classes (SSRIs, SNRIs, TCAs, herbal antidepressants), (2) 14 of the most commonly prescribed individual antidepressants, and (3) short-term and long-term treatment.

METHODS

Study Population

This observational study included patients with an incident diagnosis of dementia (*ICD-10*: F01, F03, G30, F06.7) in 1,203 general practices in Germany between January 2013 and December 2017 (index date; Figure 1). Incident dementia diagnosis is defined as the time point of the first documentation of the diagnosis by a general practitioner. Inclusion criteria were age ≥ 65 years at the index date and observation period of at least 12 months prior to the index date. Patients with psychotic (*ICD-10*: F20–F25), manic (F30), bipolar (F31), or psychoactive substance use disorders (F10–F19, except for F17) prior to the index date were excluded.

Dementia patients were matched to non-dementia controls by age, sex, physician, and index year. For the controls, the index date was that of a randomly selected visit between January 2013 and December 2017 (Figure 1). In total, 62,317 dementia patients and 62,317 controls were analyzed.

Database

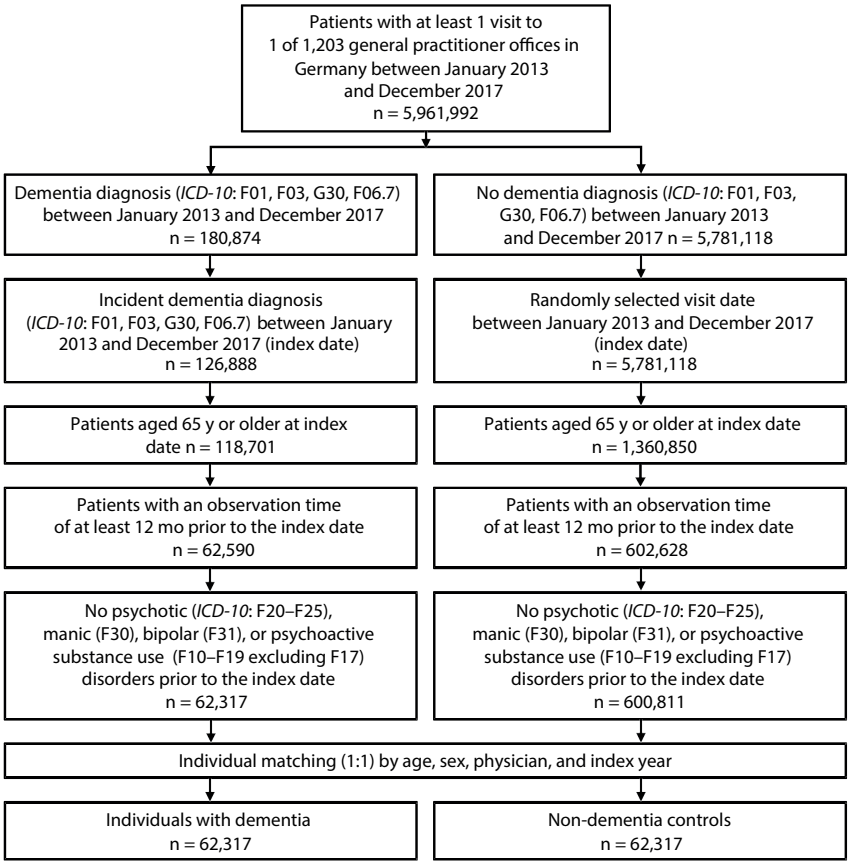
This case-control study was based on data from the German Disease Analyzer database (proprietary dataset of the contract research organization IQVIA; Frankfurt, Germany), which compiles drug prescriptions, diagnoses, basic medical and demographic data obtained directly and in an anonymous format from computer systems used in the practices of general practitioners and specialists.[45] The database covers approximately 3% of all outpatient practices in Germany. Diagnoses (according to *ICD-10*), prescriptions (according to the Anatomic Therapeutic Chemical classification system), and the quality of reported data are monitored by IQVIA. The sampling methods used to select physicians' practices are appropriate for obtaining a representative database of general and specialized practices.[45]

Because patients were queried only as aggregates and no protected health information was available for queries, according to German law, no IRB approval was required.

Study Outcomes

The main outcome of this study was the incidence of dementia as a function of the use of antidepressant drug classes (SSRIs, SNRIs, TCAs, herbal antidepressants) and most frequently prescribed antidepressants (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine, duloxetine, amitriptyline, doxepin, opipramol, trimipramine, *Hypericum perforatum*, lithium, mirtazapine). Covariates included codiagnoses associated with dementia or antidepressant drug use and were tested for between-group differences (diabetes mellitus [E10–E14], hyperlipidemia [E78], ischemic heart disease [I20–I25], hypertension [I10], heart failure [I50], renal failure [N18, N19], stroke including transient ischemic attack [I60–I64, G45], intracranial injury [S06], epilepsy [G40, G41], Parkinson's disease [G20, G21],

Figure 1. Selection of Study Patients



osteoporosis [M80, M81], rheumatoid arthritis [M05, M06], depression [F32, F33] of varying severity [F32.0–F32.3, F33.0–F33.3], depression without severity information [F32.8, F32.9, F33.8, F33.9], anxiety [F41], adjustment disorder [F43], and somatoform disorder [F45]). Due to prescription practice for antidepressants in Germany, the status of health insurance coverage was also examined. Each codiagnosis relevant to dementia or antidepressant use was used equally weighted as a binary variable (with values yes = 1 or no = 0) in both regression analyses.

Statistical Analyses

Differences in the sample characteristics between those with and those without dementia were tested using χ^2 tests for categorical variables and Wilcoxon tests for continuous variables. Two logistic regression models were then conducted to study the association between antidepressant use and dementia incidence after adjusting for covariates (health insurance status and codiagnoses associated with dementia or antidepressant use). In the first model, general treatment effects of antidepressants were analyzed (ever used vs never used). To investigate effects of treatment duration on dementia risk, the study sample was divided by median split (median = 710 days of treatment duration) into short-term and long-term antidepressant treatment groups in the second model. Treatment duration was defined as the number of days starting from the first prescription date of the defined individual antidepressant or drug class to the last day of supply with the last prescription.

Due to the large number of covariates in the regression models, Bonferroni correction was carried out to counteract the problem of α error accumulation, resulting in $P \leq .001$ being considered statistically significant. Analyses were carried out using SAS version 9.4 (SAS Institute; Cary, North Carolina; release date: July 2013).

RESULTS

Basic Characteristics of the Study Sample

The present observational study included 62,317 patients with and 62,317 patients without dementia. The basic characteristics of the study patients are displayed in Table 1 (mean [SD] age = 80.9 [6.9] years; 60.9% women). Dementia patients had private health insurance coverage less frequently than non-dementia controls (5.3% vs 9.6%, $P \leq .001$). Diagnoses associated with dementia or antidepressant use differed significantly between dementia patients and controls ($P \leq .001$) in all but one instance (ischemic heart disease: $P = .005$). Most importantly, since the rate of having depression was much higher in dementia patients compared to controls (31.1% vs 24.0%, $P \leq .001$), and depression was thus associated with an increased dementia risk (odds

Table 1. Basic Characteristics of the Study Sample After 1:1 Matching by Age, Sex, Physician, and Index Year[a]

Variable	Patients With Dementia (n = 62,317)	Patients Without Dementia (n = 62,317)	*P* Value
Sociodemographic Variables			
Age, mean (SD), y	80.9 (6.9)	80.9 (6.9)	1.000
65–69 y	4.8	4.8	
70–79 y	38.6	38.6	
80–89 y	45.2	45.2	
≥ 90 y	11.5	11.5	
Women	60.9	60.9	1.000
Men	39.1	39.1	
Private health insurance coverage	5.3	9.6	< .001
Statutory health insurance coverage	94.7	90.4	
Variables Associated With Dementia (diagnoses documented prior to index date)[b]			
Diabetes mellitus (E10–E14)	40.3	35.2	< .001
Hyperlipidemia (E78)	55.7	58.6	< .001
Ischemic heart disease (I20–I25)	38.0	37.3	.005
Hypertension (I10)	80.6	81.8	< .001
Heart failure (I50)	26.4	22.8	< .001
Renal failure (N18, N19)	19.8	15.8	< .001
Stroke including TIA (I60–I64, G45)	28.9	23.7	< .001
Intracranial injury (S06)	2.0	1.4	< .001
Epilepsy (G40, G41)	3.0	1.7	< .001
Parkinson's disease (G20, G21)	4.5	2.7	< .001
Osteoporosis (M80, M81)	19.7	18.9	< .001
Rheumatoid arthritis (M05, M06)	5.2	4.9	< .001
Variables Associated With Antidepressant Drug Use (diagnoses documented prior to index date)			
Depression (F32, F33)	31.1	24.0	< .001
Mild depression (F32.0, F33.0)	1.6	1.4	.001
Moderate depression (F32.1, F33.1)	4.3	3.4	< .001
Severe depression (F32.2, F32.3, F33.2, F33.3)	2.1	1.3	< .001
Depression without severity information (F32.8, F32.9, F33.8, F33.9)	23.2	18.0	< .001
Anxiety disorder (F41)	9.9	7.4	< .001
Adjustment disorder (F43)	9.7	8.8	< .001
Somatoform disorder (F45)	16.8	15.7	< .001

[a]Values are shown as percentages unless otherwise indicated.
[b]Diagnoses made according to *ICD-10* criteria (*ICD-10* codes shown in parentheses).
Abbreviation: SD = standard deviation.

ratios [ORs] = 1.26–1.78 for depression of varying severity, $P \leq .001$ for all), a significantly higher number of dementia patients were treated with antidepressants. To minimize bias by indication, depression was integrated as a covariate into both adjusted logistic regression models among others.

Association Between Antidepressant Drug Classes and the Risk of Developing Dementia

Table 2 presents the proportions of dementia patients and controls who received different antidepressants grouped into 4 major antidepressant drug classes (SSRIs, SNRIs, TCAs, herbal antidepressants).

In an overall comparison of antidepressant drug classes, the results of the first adjusted logistic regression model (ever vs never used) revealed that (1) SSRIs (OR = 1.29; 95% CI, 1.24–1.35; $P \leq .001$) and SNRIs (OR = 1.33; 95% CI, 1.14–1.31; $P \leq .001$) were significantly associated with an increase in dementia incidence, whereas (2) use of TCAs (OR = 0.83; 95% CI, 0.80–0.86) and herbal antidepressants (OR = 0.80; 95% CI 0.74–0.86) was significantly associated with a decreased dementia risk (Figure 2).

Association Between Individual Antidepressants and the Risk of Developing Dementia

The first adjusted logistic regression model was also used to address the general impact of individual antidepressants (ever vs never used; Figure 2). Among SSRIs, an increased dementia risk was identified exclusively for citalopram (OR = 1.33; 95% CI, 1.27–1.40; $P \leq .001$). All remaining associations with SSRIs did not reach significance. Furthermore, neither individual SNRI (ie, venlafaxine and duloxetine) exerted any significant influence on the risk of developing dementia. All TCAs (amitriptyline: OR = 0.91; 95% CI, 0.86–0.95; doxepin: OR = 0.82; 95% CI, 0.77–0.88; opipramol: OR = 0.83; 95% CI, 0.78–0.87; trimipramine: OR = 0.87; 95% CI, 0.81–0.93; $P \leq .001$ for all) and *Hypericum perforatum* as an herbal antidepressant (OR = 0.77; 95% CI, 0.72–0.83; $P \leq .001$) were associated with a decreased dementia incidence. For other frequently prescribed antidepressants, no association was found for lithium (OR = 1.37; 95% CI, 1.01–1.86; $P = .043$), but a higher dementia rate was associated with treatment with mirtazapine (OR = 1.14; 95% CI, 1.08–1.19; $P \leq .001$).

Association Between Short-Term and Long-Term Antidepressant Treatment and the Risk of Developing Dementia

To analyze the hypothesized effect of treatment duration on dementia risk, we further divided antidepressant use by median-split into short-term (< 710 days, ie, approximately 2 years or less) and long-term (≥ 710 days) treatment groups in the second adjusted logistic regression model (Table 2, Figure 3).

In general, SSRIs and SNRIs were associated with increased dementia rates with short-term treatment (SSRIs: OR = 1.42; 95% CI, 1.35–1.50; SNRIs: OR = 1.25; 95% CI, 1.14–1.37). These effects were attenuated by long-term therapy (SSRIs: OR = 1.18; 95% CI, 1.10–1.27; SNRIs: OR = 1.16; 95% CI, 1.00–1.37), but still yielded significant negative effects. In TCAs, the risk of developing dementia was significantly reduced by long-term treatment (OR = 0.78; 95% CI, 0.75–0.82), whereas short-term treatment (< 2 years) did not lead to any significant effect (OR = 1.03; 95% CI, 0.99–1.07). Short-term treatment with herbal antidepressants was associated with a significantly lowered dementia incidence (OR = 0.86; 95% CI, 0.79–0.93), which further decreased with long-term treatment (OR = 0.59; 95% CI, 0.51–0.69).

Investigation of individual substances found a similar pattern (Figure 3), in which long-term

Table 2. Proportions of Patients With and Without Dementia Who Received Antidepressant Therapy in General Practices in Germany[a]

Variable	Patients With Dementia (total n = 62,317), n (%)	Patients Without Dementia (total n = 62,317), n (%)
Antidepressant Drug Classes		
SSRI	6,279 (10.08)	4,062 (6.52)
Short term	4,234 (6.79)	2,590 (4.16)
Long term	2,045 (3.28)	1,472 (2.36)
SNRI	1,683 (2.70)	1,120 (1.80)
Short term	1,201 (1.93)	783 (1.26)
Long term	482 (0.77)	337 (0.54)
TCA	13,077 (20.98)	11,655 (18.70)
Short term	7,794 (12.51)	6,431 (10.32)
Long term	5,283 (8.48)	5,224 (8.38)
Herbal antidepressants	1,602 (2.57)	1,779 (2.85)
Short term	1,321 (2.12)	1,367 (2.19)
Long term	281 (0.45)	412 (0.66)
Individual Antidepressants		
Citalopram (SSRI)	4,796 (7.70)	2,965 (4.76)
Short term	3,347 (5.37)	2,025 (3.25)
Long term	1,449 (2.33)	940 (1.51)
Escitalopram (SSRI)	675 (1.08)	437 (0.70)
Short term	586 (0.94)	328 (0.53)
Long term	89 (0.14)	109 (0.17)
Fluoxetine (SSRI)	350 (0.56)	285 (0.46)
Short term	264 (0.42)	208 (0.33)
Long term	86 (0.14)	77 (0.12)
Paroxetine (SSRI)	375 (0.60)	328 (0.53)
Short term	260 (0.42)	215 (0.35)
Long term	115 (0.18)	113 (0.18)
Sertraline (SSRI)	721 (1.16)	519 (0.83)
Short term	535 (0.86)	370 (0.59)
Long term	186 (0.30)	149 (0.24)
Venlafaxine (SNRI)	1,001 (1.61)	641 (1.03)
Short term	703 (1.13)	446 (0.72)
Long term	298 (0.48)	195 (0.31)
Duloxetine (SNRI)	738 (1.18)	532 (0.85)
Short term	568 (0.91)	399 (0.64)
Long term	170 (0.27)	133 (0.21)
Amitriptyline (TCA)	3,809 (6.11)	3,569 (5.73)
Short term	2,678 (4.30)	2,435 (3.91)
Long term	1,131 (1.81)	1,134 (1.82)
Doxepin (TCA)	2,000 (3.21)	2,081 (3.34)
Short term	1,335 (2.14)	1,308 (2.10)
Long term	665 (1.07)	773 (1.24)
Opipramol (TCA)	3,623 (5.81)	3,707 (5.95)
Short term	2,504 (4.02)	2,494 (4.00)
Long term	1,119 (1.80)	1,213 (1.95)
Trimipramine (TCA)	1,839 (2.95)	1,793 (2.88)
Short term	1,249 (2.00)	1,147 (1.84)
Long term	590 (0.95)	646 (1.04)
Hypericum perforatum (herbal antidepressant)	1,597 (2.56)	1,774 (2.85)
Short term	1,317 (2.11)	1,365 (2.19)
Long term	280 (0.45)	409 (0.66)
Lithium (other)	123 (0.20)	66 (0.11)
Short term	55 (0.09)	31 (0.05)
Long term	68 (0.11)	35 (0.06)
Mirtazapine (other)	4,674 (7.50)	3,619 (5.81)
Short term	3,467 (5.56)	2,361 (3.79)
Long term	1,207 (1.94)	988 (1.59)

[a]Short term = treatment duration < 2 years, long term = treatment duration ≥ 2 years.

Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

treatment was associated with lower dementia incidence when compared with short-term treatment in the majority of cases. Here, the most pronounced differences were found for escitalopram (Δ OR for long-term from short-term treatment with escitalopram = 0.75). Furthermore, the lowest dementia incidence rates were documented for long-term treatment with *Hypericum perforatum* (OR = 0.60; 95% CI, 0.51–0.70; $P \leq .001$), escitalopram (OR = 0.66; 95% CI, 0.50–0.89; $P = .006$), and all TCAs (doxepin: OR = 0.72; 95% CI, 0.65–0.81; trimipramine: OR = 0.75; 95% CI, 0.67–0.84; opipramol: OR = 0.77; 95% CI, 0.70–0.84; amitriptyline: OR = 0.81; 95% CI, 0.74–0.88; $P \leq .001$ for all).

Therefore, long-term treatment with such antidepressants as escitalopram, SNRIs, or mirtazapine either reversed increased risk rates to a level of antidepressant nonusers or further decreased dementia incidence below the rate of nonusers (for TCAs: drug class and individual TCAs; for herbal antidepressants: drug class and *Hypericum perforatum*). As illustrated in Figure 3, the same pattern of a reduction in dementia incidence by long-term versus short-term treatment was determined for 17 of 18 comparisons (lithium as the only exception).

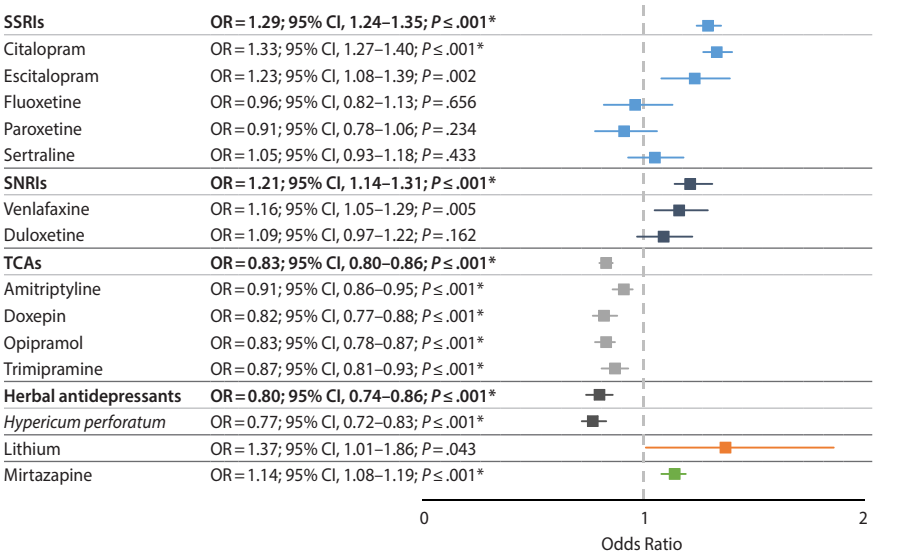
DISCUSSION

In this retrospective analysis of longitudinal-observational data, we showed that long-term antidepressant treatment (≥ 2 years) with the majority of the most commonly prescribed antidepressants (17 of 18 substances or classes) was associated with a reduction in dementia incidence compared to short-term treatment. To the best of our knowledge, this is the first study to evaluate the impact of different antidepressant drug classes and individual antidepressants on the risk of developing dementia in a time-dependent manner. The positive effects of long-term treatment found here were most pronounced for escitalopram, TCAs, and *Hypericum perforatum*. By implementing covariates associated with dementia or antidepressant use, the impact of comorbidities, such as depression, should be attenuated, and results should rather reflect effects of antidepressant use.

Strengths and Limitations

The IQVIA Disease Analyzer database longitudinally covers time spans of up to 26 years (1992–2018), has already been used for publications in various international journals with multifaceted topics, comprises about 2,500 practices with approximately 20 million patients, and contains closely monitored data. Overall, it can be regarded as a representative data collection of primary health care in Germany.[45] In this study, sample sizes of 62,317 dementia patients and 62,317 controls allowed for in-depth analyses not only of antidepressant drug classes but also of the most commonly prescribed individual antidepressants. Until now, most studies have been based on heterogeneous substance classes—at least partly contributing to the currently inconclusive empirical body of evidence.

Figure 2. Association of Antidepressant Use With Risk of Dementia[a]



[a]Multivariate regression model 1, comparisons to no antidepressant treatment; model adjusted for comorbid diagnoses associated with dementia or antidepressant use, and health insurance coverage.
*Statistically significant.
Abbreviations: OR = odds ratio, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Most importantly, in our analyses, depression and other comorbidities associated with dementia have been included as covariates to mitigate bias by indication. Nonadjustment for depression and depression-mediated effects may explain missing, negative, or otherwise conflicting results in previous studies.

The limitations of the present work are mostly related to its nature as a registry-based study, prohibiting causal inference in the absence of experimental manipulation and allowing only for discerning associations. These restrictions also affect concomitant medication records and medical history prior to database entry. Furthermore, over-the-counter (OTC) sales, eg, for *Hypericum perforatum* or *Ginkgo biloba* products, were not surveyed. In this study, we primarily used categorical variables due to structure of our dataset and the high number of covariates. Discrete data can be criticized due to a reduced sensitivity and limited analysis methods concerning sources of variation if compared to continuous data. More continuous information should be integrated in future analyses of routine datasets (eg, for antidepressant use) to allow for more precise conclusions. As in comparable studies, more detailed information on depression history or prior treatment is not available. Especially for early- versus late-onset depression, different biological mechanisms have been suggested, resulting in different associations with dementia.[7] In this respect, early-onset depression may denote a long-term risk factor whereas late-onset depression may be a prodrome of dementia in a subphenotype of cases. Accordingly, it is not possible to rule out completely that our results reflect a potential disproportion in prodromal dementia burden by depression rather than protective effects of long-term antidepressant therapy. Altogether, characteristics of depression such as timing and type of depression and severity and number of episodes as indicators of accumulating disease pathology may have an impact on the risk of developing dementia.[10] Furthermore, it is still unclear whether specific subtypes of depression are connected to specific types of dementia.

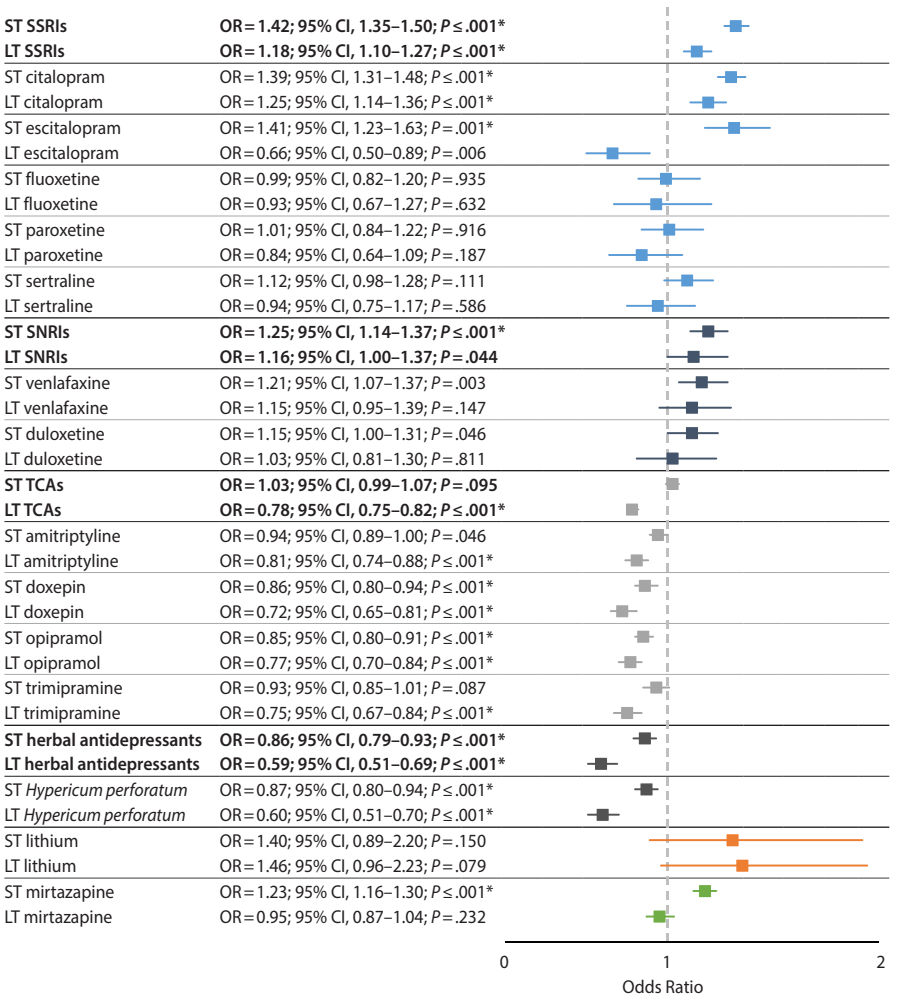
In light of the promising preclinical results of antidepressants on AD pathology, a subgroup analysis of AD dementia would have been of great interest. Unfortunately, sample sizes of AD dementia patients were too small, thus preventing such analyses, so that our results are restricted to all-cause dementia.

Accordingly, additional information on depression history and dementia subtypes would have helped to better understand the differential effects of antidepressants. As an alternative, we statistically tried to attenuate the confounding effects of depression on the risk of developing dementia, thereby focusing more on the pharmacologic effects of antidepressants alone. Still, even with depression as a covariate, the variables "depression" and "antidepressant therapy" cannot be completely statistically separated.

Differential Effects of Antidepressant Treatment

In line with previous findings,[29–32,34,36] we found elevated risks of developing dementia associated with SSRI and SNRI treatment, especially with short-term treatment. This is surprising, since a compelling body of preclinical evidence has suggested that SSRIs may reduce amyloid plaque burden and may positively affect neuroinflammation, acetylcholine release, neurodegeneration, or neurogenesis, all of which are factors relevant to dementia.[3,7,46] Furthermore, clinical

Figure 3. Association Between the Duration of Antidepressant Treatment (Short Term [ST; < 2 years] and Long Term [LT; ≥ 2 years]) and Risk of Dementia[a]



[a]Multivariate regression model 2, comparisons to no antidepressant treatment; model adjusted for comorbid diagnoses associated with dementia or antidepressant use, and health insurance coverage.
*Statistically significant.
Abbreviations: OR = odds ratio, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRIs = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

trials with fluoxetine[24] and sertraline[23] reported positive outcomes. However, other SSRI trials revealed negative results, but started treatment in an advanced disease stage, administered SSRIs only for short time spans, and used insensitive cognitive screening as outcomes.[16–22] Some epidemiologic/registry-based studies also showed results in favor of SSRI treatment.[37,38,44] In summary, clinical data have been inconclusive and require further clarification. A rationale for SNRI treatment in dementia prevention can be deduced from the well-documented pathologic hallmark of neurodegeneration of the locus ceruleus, resulting in low levels of norepinephrine.[47] However, a recent review[48] suggests that changes of the integrity of the noradrenergic system instead of reduced norepinephrine input might be a key contributor driving AD pathology and might at least partly explain why SNRIs failed to exert protective or preventive effects. From this point, it also seems logical that different pharmaceutical compounds with different modes of action—even if assigned to the same drug class—exert different effects on different molecular targets. As such, the impact of individual antidepressants on the risk of developing dementia should be investigated rather than the outcomes of heterogeneous antidepressant drug classes.

Regarding individual SSRIs, the overall negative effect of SSRIs seems to be mainly attributable to citalopram. In contrast, long-term escitalopram treatment yielded the lowest risk estimates for developing dementia as similarly described by Burke et al,[40] even if level of significance was narrowly missed due to a conservative correction for multiple comparisons. This finding is remarkable because citalopram is a mixture of the two stereoisomers *S*- and *R*-citalopram while escitalopram contains the therapeutically active *S*-enantiomer only. Thus, both share 50% of their composition. Furthermore, preclinical and favorable results

are mostly based on treatment with both compounds, citalopram[11–13,15] and escitalopram.[14] Also, additional analyses on differences between these two groups did not contribute to the understanding of the dissociated effects of escitalopram and citalopram: No significant sex differences along with a clinically irrelevant age difference were found between citalopram (81.2 years) and escitalopram users (80.3 years, $P \leq .001$; relevant comorbidities and health insurance coverage were adjusted for in both regression models). Taken together, these diverging findings may indicate a differential response of different clinical subphenotypes or may point to the involvement of specific target polymorphisms.

For TCAs in general and for individual TCAs, we detected a reduced risk of developing dementia, especially with long-term treatment. At first glance, this finding seems counterintuitive since TCAs—due to their anticholinergic properties—are known for neuropsychiatric complications, ranging from cognitive decline to delirium.[49–51] Accordingly, a recent nested case-control study[52] reported an increased risk of dementia associated with the long-term use of anticholinergic drugs, including antidepressants. However, in the group of anticholinergic antidepressants, TCAs and SSRIs with anticholinergic activity were intermixed. Epidemiologic or registry studies comparing different antidepressant drug classes also revealed no[33,37] or detrimental effects of TCAs.[29–32] Bartels et al[44] reported an accelerated progression of MCI to dementia in a non-SSRI treatment group, but this group combined TCAs, SNRIs, and other non-SSRI antidepressants. Nevertheless, similar results showing a reduction of dementia incidence by TCAs were also observed by others.[34,35,43] In this context, it is also noteworthy that TCAs are most commonly prescribed in low dosages for sleeping difficulties in clinical practice, potentially reflecting subsyndromal to mild depressive states. Poor sleep has been shown to negatively affect the glymphatic clearance of amyloid-β peptides,[53] a mechanism that may be targeted by antidepressants like TCAs, thereby attenuating the risk of developing dementia. In contrast, Kessing[10] hypothesized that long-term TCA therapy may prevent progression to dementia in severe depression,[43] whereas continued treatment with SSRIs or newer non-SSRIs may be beneficial for less severe depressive disorders.[10,42] Taken together, both observations may suggest a differential response of specific depression subphenotypes to antidepressants.

Among herbal antidepressants, *Hypericum perforatum* was strongly and consistently associated with a reduced risk of developing dementia with short-term and long-term therapy. In preclinical studies,[54–57] *Hypericum perforatum* has been shown to exert antioxidative and anti-inflammatory effects, to attenuate amyloid-β-mediated toxicity, and to reverse amyloid-β accumulation. As a potential causal link between depression and dementia, *Hypericum perforatum* directly activates the ABCC1 transporter, one of the major β-amyloid–exporting molecules at the blood-brain barrier.[58,59] Interestingly, recent evidence has indicated that citalopram also demonstrates a high affinity to the ABCC1 transporter.[60] Accordingly, the potential dementia-preventive, long-term treatment effects of *Hypericum perforatum* and escitalopram—as the therapeutically active *S*-enantiomer of citalopram—may be promoted by increased brain amyloid-β peptide efflux due to ABCC1 transporter activation. Further investigations have to analyze in more detail how additional parameters might mediate these potentially protective effects. This is of particular importance, since *Hypericum perforatum*, as a typical OTC drug, is usually prescribed for less severely depressed patients. Thus, low depression severity and other protective characteristics could have biased the results for *Hypericum perforatum* in terms of a favorable treatment effect. Clearly, further empirical research has to be done before any conclusion for clinical practice should be drawn in this matter.

In recent years, hypothesized neuroprotective effects of lithium through inhibition of glycogen synthase kinase 3 (GSK-3) have been explored. For example, Kessing et al[61] reported that continued lithium treatment normalized dementia rates. Since lithium is mainly used to treat bipolar disorders, and subjects with bipolar disorders were excluded in the present study, this selection or indication bias might—at least partly—explain the absence of a protective effect on the risk of developing dementia. Concordantly, Angst et al[62] investigated a mixed group of bipolar and unipolar depressed patients and failed to present a preventive effect of lithium on dementia. However, the long-term use of lithium was also found to positively influence clinical and cerebrospinal fluid biomarkers in amnestic MCI without any affective disorder.[63] Still, in this clinical trial,[63] lithium was administered to reach only subtherapeutic concentrations, also limiting comparability to our naturalistic data.

Effects of Antidepressant Treatment Duration

For all but 1 comparison, our data showed that long-term treatment with any antidepressant was associated with lower dementia rates than short-term treatment. This finding is in accordance with previous studies[42,43] of Danish registry data analyzing the effects of continued antidepressant treatment. Recently, long-term SSRI treatment (>4 years) has been reported to potentially delay progression from MCI to AD dementia.[44] An exploratory analysis also yielded similar long-term treatment effects for all but 1 antidepressant when a cutoff of 4 treatment years was used (data not shown). Here, we additionally provide data for the impact of individual antidepressants and found that (1) long-term treatment with escitalopram, SNRIs, or mirtazapine is linked to risk rates at levels of nonusers and (2) long-term treatment with *Hypericum perforatum* and TCAs is associated with decreased dementia incidence (below rates of nonusers). Moreover, our observation of positive long-term treatment effects (≥2 years) may explain why most randomized clinical trials—mostly testing antidepressants for only several weeks—failed to find similar results. On the downside, there is considerable evidence in geriatric depression that maintenance of antidepressant therapy with TCAs, SNRIs,[64] and SSRIs[65] finally led to response,

remission, or significantly reduced recurrence of depression and thereby reduced emergence of treatment resistance. These findings might be of importance in the present context since the recurrence of depressive episodes[7] and subsequent treatment resistance could additionally enhance the risk of developing dementia. Besides lower mortality risks,[66] long-term (and improved) depression treatment may contribute to dementia risk modification (1) by addressing cellular and molecular drivers of pathological aging and (2) by enabling depressed patients to better engage in their treatment and adopt favorable lifestyle behaviors.

It remains a question for future research which additional characteristics—eg, different subphenotypes or genetic polymorphisms—distinguish short-term from long-term users. It may be hypothesized that antidepressant treatment was discontinued prematurely because of remission of depressive symptoms or side effects and, thus, antidepressants were not able to exert their potentially protective effects.

Clinical Implications and Conclusions

Our findings—especially for long-term antidepressant treatment—may bear important clinical implications. The availability of a secondary prevention strategy notably delaying progression to AD dementia could contribute to an overall lower prevalence of AD dementia with a concomitant impact on public health and health care costs. Continuation of antidepressant treatment may be considered with all due caution in elderly patients with depression, even beyond remission, not only for depressive relapse prevention but also in the context of possible secondary dementia prevention. In particular, tricyclic antidepressants, *Hypericum perforatum*, and escitalopram were associated with a reduced dementia incidence in the present study and may serve as potential candidate compounds to be further pursued for proof-of-concept studies of long-term treatment in geriatric depression.

Clinical trials—although well acknowledged as the gold standard procedure—have debunked numerous promising compounds and become increasingly challenging with longer treatment durations. Thus and in awareness of the controversy of this suggestion, analyzing data from registries in a naturalistic setting may be an attractive and feasible alternative. If individual datasets could be combined in a multinational effort, even more powerful analyses of merged big databases could be performed and an additive contribution with naturalistic data could be made.

Submitted: December 10, 2019; accepted April 21, 2020.

Published online: August 25, 2020.

Author contributions: All authors contributed to the conception and design of the research and interpretation of the data and provided critical revision of the manuscript for important intellectual content. Dr Bartels drafted the manuscript. Dr Kostev performed statistical analysis and had full access to all of the data in the study. Drs Wiltfang and Kostev contributed equally to the work as senior authors. All authors gave approval for the final version of the manuscript to be published.

Potential conflicts of interest: All authors report no financial relationships with commercial interests related to this article. Beyond that, **Dr Bartels** receives honoraria as a diagnostic consultant for Boehringer Ingelheim. **Dr Bohlken** received honoraria from Firma Dr Willmar Schwabe and the Berufsverband Deutscher Nervenärzte (BVDN). **Dr Wiltfang** is supported by an Ilídio Pinho professorship, iBiMED (UID/BIM/04501/2013), and FCT project PTDC/DTP_PIC/5587/2014 at the University of Aveiro, Portugal; is an advisory board member of Abbott, Boehringer Ingelheim, Immunogenetics, Lilly, Merck Sharp & Dohme (MSD), and Roche Pharma; received honoraria for lectures from the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP), Actelion, Amgen, CSF-Society, Helios Klinikum Wuppertal, Janssen-Cilag, Med Update, Pfizer, Roche Pharma, and Vitos Kurhessen-Bad Emstal as well as funding from the German Federal Ministry for Education and Research (BMBF), the European Union (EU), and the German Research Foundation (DFG); and holds the following patents: PCT/EP 2011 001724 and PCT/EP 2015 052945. **Dr Kostev** is an employee of IQVIA and has no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding/support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Additional information: Original datasets from the German Disease Analyzer database (owned and maintained by IQVIA) are not publicly available. Analysis data are available on reasonable request from Dr Kostev (karel.kostev@iqvia.com).

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