Use of Selective Serotonin Reuptake Inhibitors and Risk of Upper Gastrointestinal Tract Bleeding

A Population-Based Cohort Study

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Background: Selective serotonin reuptake inhibitors (SSRIs) have been suspected of increasing the risk of bleeding. We examined the risk of upper gastrointestinal tract (GI) bleeding with use of antidepressant medication.

Methods: All users of antidepressants in the county of North Jutland, Denmark, from January 1, 1991, to December 31, 1995, were identified in the Pharmaco-Epidemiologic Prescription Database of North Jutland. In the Hospital Discharge Register, hospitalizations for upper GI bleeding were searched among the 26 005 users of antidepressant medications and compared with the number of hospitalizations in the population of North Jutland who did not receive prescriptions for antidepressants.

Results: During periods of SSRI use without use of other drugs associated with upper GI bleeding, we observed 55 upper GI bleeding episodes, which was 3.6 times more than expected (95% confidence interval, 2.7-4.7), corresponding to a rate difference of 3.1 per 1000 treatment years. Combined use of an SSRI and nonsteroidal anti-inflammatory drugs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1-19.5) and 5.2 (95% confidence interval, 3.2-8.0), respectively. Non-SSRIs increased the risk of upper GI bleeding to 2.3 (95% confidence interval, 1.5-3.4), while antidepressants without action on the serotonin receptor had no significant effect on the risk of upper GI bleeding. The risk with SSRI use returned to unity after termination of SSRI use, while the risks were similarly increased during periods of use and nonuse of non-SSRIs.

Conclusion: Selective serotonin reuptake inhibitors increase the risk of upper GI bleeding, and this effect is potentiated by concurrent use of nonsteroidal anti-inflammatory drugs or low-dose aspirin, whereas an increased risk of upper GI bleeding could not be attributed to other types of antidepressants.

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DURING THE 1990s, the newer more receptor-selective antidepressive agents were used increasingly, partly because of their relatively few adverse effects and low toxicity. Several clinical reports have indicated an association between use of all types of the selective serotonin reuptake inhibitors (SSRIs) and bleeding disorders, ranging from prolonged bleeding time, ecchymoses, purpura, and epistaxis[1-10] to more serious conditions, such as gastrointestinal (GI) tract, genitourinary tract, and intracranial bleeding.[1,11] Release of serotonin by platelets plays an important role in hemostasis, and serotonin is taken up from the blood stream by serotonin transporters, similar to those transporting serotonin in the brain.[12] Because platelets are not capable of synthesizing serotonin, depletion of serotonin stores could induce hemorrhagic complications. The older antidepressants, the tricyclic and tetracyclic agents, have differing degrees of selectivity on the serotonin receptor relative to the other monoamine receptors,[13] and some of them may also interfere with hemostatic function.

A recent case-control study[14] indicated an increased risk of upper GI bleeding in users of SSRIs and, to a lesser degree, some other antidepressants. We investigated the risk of upper GI bleeding in users of SSRIs and other antidepressants in a population-based cohort study including all residents in a county of northern Denmark during a 5-year period.

METHODS

The study was conducted within the 490 000 inhabitants of North Jutland County, Denmark, from January 1, 1991, to December 31, 1995. The National Health Service provides tax-supported health care for all inhabitants, guaranteeing free access to family physicians, public hospitals, and clinics and refunding a variable proportion (usually 50%-75%) of the

costs of drugs prescribed by physicians. The population-based Pharmaco-Epidemiologic Prescription Database of North Jutland,[15] initiated on January 1, 1991, retains key information on prescriptions for refundable drugs dispensed from all 33 pharmacies in the county. This includes the personal identification number of the customer, the type of drug according to the Anatomical Therapeutical Chemical classification system,[16] and the date of prescription (date of dispensing the drug). The 10-digit personal identification number (which encodes sex and date of birth) ensured that a complete prescription history could be established for each individual.

The antidepressant compounds included in the present study were classified into 3 groups according to their inhibitory action on the serotonin reuptake mechanism: SSRIs, non-SSRIs, and other antidepressants. We included clomipramine hydrochloride in the group of SSRIs because of its potent and rather selective blockage of serotonin transport.[13,17] The group of non-SSRIs included antidepressants with a balanced action on serotonin and norepinephrine reuptake mechanisms,[13,18] while the group of other antidepressants included antidepressants with either a selective inhibitory action on norepinephrine uptake (nortriptyline hydrochloride, desipramine hydrochloride, trimipramine, maprotiline, and amoxapine) or no action on any reuptake mechanism (mianserin hydrochloride).[13]

We identified 30 496 users of antidepressants in the Pharmaco-Epidemiologic Prescription Database of North Jutland. Antidepressant medicine in Denmark is only available at pharmacies if the patient has a prescription from a physician. Record linkage with the Danish mortality files resulted in the exclusion of 33 persons (0.1%) because of date of death before the date of antidepressant prescription or an error in the personal identification number. We excluded 48 users (0.2%) who were younger than 16 years or older than 105 years at the date of antidepressant prescription and 1255 users (4%) who were not residents in the county. The remaining 29160 persons were linked to the county Hospital Discharge Register, which retains key information at the individual level for all hospitalizations in the county from January 1, 1977, through December 31, 1995.[19] Information in the Hospital Discharge Register includes the identification number of the patient, the date of discharge, and up to 20 discharge diagnoses,[19] coded according to the Danish version of the *International Classification of Diseases, Eighth Revision (ICD-8)*, until the end of 1993 and according to the 10th revision since.[19] Based on the hospital discharge history, we excluded an additional 427 persons (1%) diagnosed as having upper GI bleeding (ie, bleeding caused by a gastric, duodenal, or gastrojejunal ulcer, hematemesis, or melena) and 1054 persons (4%) diagnosed as having a medical condition predisposing to GI bleeding (alcoholism, esophageal varices, Mallory-Weiss syndrome, or liver cirrhosis) between 1977 and before the date of the first notified antidepressant prescription. After linkage to the Danish Cancer Registry,[20] 1674 subjects (6%) were excluded because they had cancer, another predisposing condition to GI bleeding, after 1980 (all cancer types except nonmelanoma skin cancer) and before the first antidepressant prescription. Thus, a total of 26 005 persons were included in the study.

PERSON-YEARS AT RISK

The follow-up for hospitalization of upper GI bleeding began on the date of the first notified prescription of antidepressants and ended on the date of a first admission to the hospital for GI bleeding or for one of the medical conditions that predispose to GI bleeding (alcoholism, esophageal varices, Mallory-Weiss syndrome, liver cirrhosis, or cancer), the date of death, or December 31, 1995, whichever occurred first. The follow-up period of cohort members was then subdivided into periods of use of antidepressants (current exposure), lasting from the date of prescription until 90 days thereafter (or a censoring date), and periods of nonuse of antidepressants (former exposure), extending from 90 days after a prescription to the date of the next prescription (or a censoring date). The period of 90 days was chosen because antidepressants are mainly prescribed in packets for 3-month use. Furthermore, periods of use and nonuse were flagged if cohort members received prescriptions at the same time of 1 or more other drugs suspected of causing GI bleeding: nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin, high-dose aspirin, vitamin K antagonist, or oral corticosteroids, again applying the 90-day rule. Periods of antidepressant use, to which all 26 005 persons contributed follow-up time, were further divided into periods of only SSRI use, only non-SSRI use, or only other antidepressant use and periods of exposure to antidepressant categories in combination with one of the supposedly predisposing drugs. Periods of former use were similarly subdivided into periods of use or of no use of any of the other drugs predisposing to GI bleeding.

To evaluate the possible association further, a subanalysis restricted the cohort to 14 221 persons with no previous exposure to any of the other drugs predisposing to GI bleeding before their first notified prescription for antidepressant medication; in the analysis, use of the other predisposing drugs led to termination of follow-up. The follow-up period was divided into periods of only SSRI use, only non-SSRI use, or only other antidepressant use and corresponding periods of former use when none of the antidepressants considered were used.

CALCULATION OF OBSERVED-EXPECTED RISK RATIOS

The observed-expected ratio was calculated as the observed number of hospitalizations for upper GI bleeding divided by the expected number. The comparison population was the inhabitants of North Jutland County who had not received a prescription for antidepressants or any of the other drugs thought to cause upper GI bleeding and who had not been hospitalized between January 1, 1977, and December 31, 1995, with upper GI bleeding or with a medical condition predisposing to upper GI bleeding. First-time hospitalization rates for upper GI bleeding were calculated for this background population according to sex, 5-year age groups, and 1-year calendar periods, and these rates were applied to the person-years of observation in the cohort to obtain the number of upper GI bleeding episodes expected if the users of antidepressants had experienced the same risk of hospitalization for upper GI bleeding as nonusers.

Under the assumption of an additive effect between antidepressants and other risk factors for upper GI bleeding, the rate difference was calculated as the difference between the incidence rate of upper GI bleeding among only users of antidepressants and the incidence rate in the background population not exposed to antidepressant medication.

RESULTS

Two thirds of the 26 005 individuals who used antidepressant medication at some time during the study period were women. The distribution of age and year of first prescription was similar among men and women (**Table 1**). Overall, the 26 005 users of antidepressants accumulated a total of 28 751 person-years of follow-up for current use of antidepressants and a further 29 823 person-years of follow-up after cessation of antidepressant use (former use).

Among current users of SSRIs only, 55 hospitalizations for upper GI bleeding were observed, with 15.3 expected, yielding an observed-expected ratio of 3.6 (**Table 2**). The risk of upper GI bleeding among current users of non-SSRIs only was 2.3. For current users of other antidepressants only, the risk of upper GI bleeding was not significantly increased. The rate differences for the users of only SSRIs, only non-SSRIs, and only other antidepressants were 3.1, 1.8, and 0.9 per 1000 treatment years, respectively.

In the entire county, 149 573 persons had periods with use of NSAIDs only, with 206 hospitalizations for upper GI bleeding, resulting in a risk ratio of 4.5 (95% confidence interval, 3.9-5.2), while 26 762 persons had periods with use of low-dose aspirin only, with 204 hospitalizations for upper GI bleeding, with a risk of 2.5 (95% confidence interval, 2.2-2.9) (data not shown). Use of SSRIs in combination with NSAIDs increased the risk of upper GI bleeding by more than 12 (Table 2). Concurrent use of SSRIs and low-dose aspirin increased the risk to 5.2. Use of non-SSRIs combined with NSAIDs or low-dose aspirin increased the risk to 8.2 and 4.6, respectively. Use of other antidepressants combined with NSAIDs increased the risk to 6.3, while the risk was 2.5 for combined use of other antidepressants and low-dose aspirin.

There were 13 362 users of SSRIs who had periods of former use and who were followed up through periods of no use of any of the drugs considered, with 18 GI bleeding episodes observed, corresponding to a nonsignificant slight increase in risk (Table 2). However, for former users of the 2 other categories of antidepressants, the risk did not alter considerably from that found in only users.

The risk of GI bleeding was increased for all the different types of SSRIs, although only a few cases were observed for most of the drugs (**Table 3**). The risk was also increased for all types of non-SSRIs, but slightly less than for the SSRIs. There was no risk increase for use of other antidepressants, except among users of mianserin.

When we analyzed the risk restricted to those persons using only antidepressants with no previous or intermediate use of any of the other defined drugs, the risk for hospitalization for upper GI bleeding in current SSRI users was 3.4, whereas in former SSRI users, it was 0.6 (**Table 4**). For only and former users of non-SSRIs, the risk was 2.2 and 2.0, respectively, while the risk was 1.5 and 0.5, respectively, for only and former users of other antidepressants.

Table 1. Characteristics of 26 005 Antidepressant Users in the County of North Jutland, Denmark, 1991-1995*

Characteristic	Men (n = 8314)	Women (n = 17 691)	Total Cohort (N = 26 005)
Age at first recorded prescription, y			
≤59	4440 (53)	9025 (51)	**13 465** (52)
60-69	1402 (17)	3069 (17)	**4471** (17)
≥70	2472 (30)	5597 (32)	**8069** (31)
Year of first recorded prescription			
1991	2103 (25)	5754 (33)	**7857** (30)
1992	1269 (15)	2704 (15)	**3973** (15)
1993	1397 (17)	2854 (16)	**4251** (16)
1994	1802 (22)	3364 (19)	**5166** (20)
1995	1743 (21)	3015 (17)	**4758** (18)

*Data are given as number (percentage) of individuals. Percentages may not total 100 because of rounding.

COMMENT

This follow-up of a large population in Denmark shows that users of SSRIs were hospitalized with upper GI bleeding at a rate 3.6 times greater than persons of a similar age and sex for whom these medications had not been prescribed. This corresponds to an excess of 3.1 upper GI bleeding episodes per 1000 treatment years attributable to use of SSRIs, a nonnegligible absolute risk. The risk for different types of SSRIs was similar, suggesting a class effect linked to their mechanism of action. The effect was potentiated by concurrent use of NSAIDs and, to a lesser extent, by low-dose aspirin. The group of non-SSRIs increased the risk of upper GI bleeding, although to a lesser extent than the SSRIs.

Our existing knowledge is mainly based on the case-control study by de Abajo et al,[14] including 1651 cases with GI bleeding and 10 000 matched controls. They reported a 3-fold increased risk of upper GI bleeding among users of all types of SSRIs compared with that of nonusers. An interaction between SSRIs and NSAIDs or aspirin was also observed. These findings have all been supported by our population-based cohort study.

In addition, our study supplies valuable information by computation of risk estimates for persons with no previous use of any other of the risk-increasing drugs at the time of the first recorded antidepressant prescription and no use of any of these risk-increasing drugs during or after antidepressant treatment. Our comparison group is a low-risk group (ie, they have not been prescribed any drugs thought to increase the risk of upper GI bleeding) and, therefore, is similar to the restricted subcohort. Thus, the risk estimates for antidepressant use obtained for this subcohort may actually be more correct than those obtained for the total cohort. The results indicate a causal relationship between SSRI use and risk of upper GI bleeding, because the increase in risk seemed to be confined to periods of use of SSRIs.

By contrast, the risk estimates for non-SSRI users remained rather similar for periods of use and nonuse, suggesting that other factors connected with use of non-SSRIs could contribute to the increase in risk found among non-SSRI users. Use of SSRIs in Denmark is recommended as the first choice only in patients with mild to moderate depression or in patients with severe depression without melancholic features (Danish Health Board, written communication, December 2000), whereas the tricyclic or tetracyclic antidepressants are recommended as the first-line treatment in patients with more severe depression. A difference in the severity of depression would be expected between patients treated with SSRIs and patients treated with non-SSRIs or other antidepressants. However, whether such a difference between the exposure groups also

Table 2. The O/E for Upper Gastrointestinal Tract Bleeding Among 26 005 Current Users of Antidepressant Medication in the County of North Jutland, Denmark, 1991-1995*

Variable	No. of Persons†	Person-Years at Risk	Obs	O/E (95% CI), RD‡ per 1000	Treatment Years
SSRIs					
Current use					
SSRI only	17 320	12 760.2	55	3.6 (2.7-4.7)	3.1
SSRI and NSAIDs only	4107	960.2	17	12.2 (7.1-19.5)	16.3
SSRI and low-dose aspirin only	2640	1532.9	20	5.2 (3.2-8.0)	12.4
SSRI and other drugs only	4678	1566.8	27	11.6 (7.5-16.6)	15.8
Former use					
No use of any other drug	13 362	14 465.6	18	1.2 (0.7-1.9)	0.2
Non-SSRIs					
Current use					
Non-SSRI only	7716	8804.7	27	2.3 (1.5-3.4)	1.8
Non-SSRI and NSAIDs only	2418	827.2	9	8.2 (3.7-15.5)	9.6
Non-SSRI and low-dose aspirin only	927	657.7	7	4.6 (1.8-9.4)	8.3
Non-SSRI and other drugs only	2932	1063.3	7	4.5 (1.8-9.2)	5.1
Former use					
No use of any other drug	6604	9592.4	25	2.5 (1.6-3.6)	1.6
Other Antidepressants					
Current use					
Other antidepressants only	4436	4153.7	9	1.7 (0.8-3.1)	0.9
Other antidepressants and NSAIDs only	1224	340.9	3	6.3 (1.3-18.4)	7.4
Other antidepressants and low-dose aspirin only	542	356.6	2	2.5 (0.3-9.2)	3.4
Other antidepressants and other drugs only	1979	726.7	5	5.2 (1.7-12.2)	5.6
Former use					
No use of any other drug	3927	5764.7	12	1.9 (1.0-3.3)	1.0

Abbreviations: CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; Obs, observed number of hospitalizations for upper gastrointestinal tract bleeding; O/E, observed-expected ratio; RD, rate difference; and SSRI, selective serotonin reuptake inhibitor.

*Other drugs include high-dose aspirin (N02B A01 and N02B A51), vitamin K antagonists (B01A A03 and B01A A04), and oral corticosteroids (H02A B), used alone or in combination with NSAIDs (M01A) or low-dose aspirin (B01A C06 and N02B A01). (Anatomical Therapeutical Chemical classification system codes are in parentheses.)

†The grouping of persons is not mutually exclusive; persons can contribute to more than one category of current use.

‡The RD is the difference between the incidence rate of the exposed population and the incidence rate of the unexposed population (where the unexposed population equals the relevant background population incidence).

includes lifestyle factors, especially those influencing the risk of upper GI bleeding, such as smoking or alcohol intake,[21] is not clear.

Serotonin is thought to play an important role in hemostasis, mainly through an enhancing effect on adenosine diphosphate and thrombin.[22] The SSRIs in therapeutic doses consistently deplete serotonin after several weeks of treatment.[23,24] Although adverse vascular events have been ascribed to the SSRIs in sporadic cases, studies[25-27] of hemostatic function in consecutive patients or healthy volunteers receiving SSRI treatment revealed no abnormalities in platelet aggregation, hematopoiesis, or coagulation profile. According to the hypothesis, a higher threshold for serotonin-induced bleeding would be expected in users of the non-SSRIs than in users of the SSRIs. Based on our similar risk estimates in current and former users of non-SSRIs, effects of confounding factors must be considered as more likely explanations than an effect of the non-SSRIs.

The main strength of our study is the uniformly organized health care system, allowing a population-based design and complete follow-up. Nonaspirin NSAIDs are available only by prescription, apart from low-dose ibuprofen, which is obtainable over-the-counter in Denmark. However, regular users of low-dose ibuprofen receive a 50% refund when cashing a prescription for ibuprofen. We have probably, therefore, registered most of the patients receiving NSAIDs regularly. We could not control for over-the-counter use of aspirin. However, we have no reason to believe that over-the-counter use of aspirin or ibuprofen occurred more often in the cohort than it did in our comparison group of persons not having prescriptions for antidepressants or the other drugs suspected of causing GI bleeding.

A limitation of our data is the lack of clinical detail. The diagnosis at discharge may not be entirely accurate, and upper GI bleeding may have been misclassified.[28,29] Hospitalizations outside the county of persons living in the county were not registered in the regional Hospital Discharge Register. Most hospitalizations for upper GI bleeding tend to be emergency admissions and, thus, patients will in most cases be taken to the local hospital. Emergency hospitalizations outside of the county amount to a negligible proportion, probably less than 1%. Assignment to different exposure categories was based on the dispensing date and the assumption that exposure extended 90 days from each prescription. If the compliance was not complete or the duration of use varied, the exposure would be misclassified. However, we have no reason to believe that this misclassification would be different among the 3 groups of antidepressant users. In addition, we were not able to control for smoking, alcohol intake,[21] and infection with *Helicobacter pylori*. We may expect users

Table 3. The O/E for Upper Gastrointestinal Tract Bleeding Among Only Users of Different Types of Antidepressants in the County of North Jutland, Denmark, 1991-1995

Type of Antidepressant*	No. of Persons†	Person-Years at Risk	Obs	O/E (95% CI)
SSRIs				
Fluoxetine (N06A B03)	3541	1746.1	5	3.9 (1.2-9.0)
Citalopram (N06A B04)	10 430	5697.5	35	4.1 (2.8-5.7)
Paroxetine (N06A B05)	1620	739.4	2	3.2 (0.4-11.4)
Sertraline hydrochloride (N06A B06)	861	265.0	1	4.1 (0.1-22.7)
Fluvoxamine maleate (N06A B08 and N06A E02)	612	338.9	2	4.7 (0.5-16.8)
Clomipramine hydrochloride (N06A A04)	2887	3778.9	9	2.3 (1.0-4.3)
Non-SSRIs				
Imipramine hydrochloride (N06A A02)	980	717.3	3	3.5 (0.7-10.1)
Lofepramine hydrochloride (N06A A07)	882	520.7	2	3.4 (0.4-12.3)
Amitriptyline hydrochloride (N06A A09)	3961	467.0	15	2.5 (1.4-4.1)
Doxepin hydrochloride (N06A A12)	1830	2411.8	7	2.0 (0.8-4.1)
Dothiepin hydrochloride (N06A A16)	460	421.4	0	. . .
Other antidepressants				
Desipramine hydrochloride (N06A A01)	12	17.2	0	. . .
Trimipramine (N06A A06)	60	88.4	0	. . .
Nortriptyline hydrochloride (N06A A10)	1681	1376.1	1	0.7 (0.0-3.9)
Amoxapine (N06A A17)	560	547.6	0	. . .
Maprotiline (N06A A21 and N06A C01)	891	795.5	1	1.1 (0.0-6.1)
Mianserin hydrochloride (N06A C02)	1658	1273.5	7	3.1 (1.3-6.5)

Abbreviations: CI, confidence interval; ellipses, data not applicable; Obs, observed number of hospitalizations for upper gastrointestinal tract bleeding; O/E, observed-expected ratio; and SSRI, selective serotonin reuptake inhibitor.
*Anatomical Therapeutical Chemical classification system codes are in parentheses.
†The grouping of persons is not mutually exclusive; persons can contribute to any category according to previous use of antidepressants.

Table 4. The O/E for Upper Gastrointestinal Tract Bleeding Among a Restricted Cohort of 14 221 Antidepressant Users With No Use of Any Other Drug Associated With Increased Risk of Upper Gastrointestinal Tract Bleeding in the County of North Jutland, Denmark, 1991-1995*

Status at First Prescription	No. of Persons	Person-Years at Risk	Obs	O/E (95% CI)
SSRIs				
SSRI only	7565	5837.9	20	3.4 (2.1-5.2)
No use of any other drug	5143	5854.0	3	0.6 (0.1-1.8)
Non-SSRIs				
Non-SSRI only	4375	4778.3	13	2.2 (1.1-3.7)
No use of any other drug	2875	3641.0	7	2.0 (0.8-4.2)
Other Antidepressants				
Other antidepressant only	2281	2117.1	4	1.5 (0.4-3.9)
No use of any other drug	1531	2103.0	1	0.5 (0.0-2.6)

Abbreviations: CI, confidence interval; Obs, observed number of hospitalizations for upper gastrointestinal tract bleeding; O/E, observed-expected ratio; and SSRI, selective serotonin reuptake inhibitor.
*Other drugs include nonsteroidal anti-inflammatory drugs (M01A), low-dose aspirin (B01A C06 and N02B A01), high-dose aspirin (N02B A01 and N02B A51), vitamin K antagonists (B01A A03 and B01A A04), and oral corticosteroids (H02A B), used alone or in combination. (Anatomical Therapeutical Chemical classification system codes are in parentheses.)

of antidepressants to have a higher prevalence of smoking and a higher alcohol intake.[30,31] Part of the potential effect of alcohol intake is likely to have been eliminated because we excluded all persons with alcoholism and liver cirrhosis from the study. Furthermore, some of the confounding effect of tobacco use and alcohol may have been reduced when periods of current use were compared with former use periods. In this way, each antidepressant user acted as his or her own control, and this would reduce some of the confounding effect of tobacco use, alcohol intake, and other confounding factors.

In conclusion, the findings of this study support the hypothesis of an increased risk of upper GI bleeding during use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further. The strength of the associations found and the apparent class effect, together with a plausible biological mechanism, support a possible causal relation. We interpret the increase in risk of upper GI bleeding in users of non-SSRIs cautiously because of the similarity of the risk estimates between periods of current and former use in these persons. However, more studies of the association between antidepressant drugs and upper GI bleeding are clearly warranted owing to the high prevalence of use of these drugs, resulting in an appreciable absolute risk and, thus, considerable public health implications.

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