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Early discontinuation of antidepressant treatment and suicide risk among persons aged 50 and over: a population-based register study

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Abstract

Background—As many as 47% of adults over age 50 discontinue treatment with antidepressants after redeeming only one prescription. The study aim was to assess the risk of suicide in adults aged 50+ who discontinue antidepressants at an early stage of treatment.

Method—Case control study of all individuals aged 50+ living in Denmark and who initiated antidepressant treatment between July 1st 1995 and December 31st 2000 (N=217,123). Hazard ratios were calculated using Cox regression analyses, propensity score matching techniques, and marginal structural models.

Results—During the study period, 78,594 men and 138,529 women aged 50+ began treatment with an antidepressant medication, of whom 309 men and 229 women died by suicide. Men aged 50+ who discontinued treatment early had a suicide rate of 167 per 100,000 compared with 175 per 100,000 in those who continued refilling prescriptions; hazard ratio = 0.98 [CI-95%: 0.78–1.23]. The suicide rate in women who discontinued treatment was 52 per 100,000 compared with 74 per 100,000 in those who continued refilling; hazard ratio = 0.72 [CI-95%: 0.55–0.94]. Although people with previous psychiatric hospitalizations had greater risk of suicide than those without past hospital admissions, the difference was not significant in the adjusted model.

Limitations—Prescriptions redeemed at pharmacies is our only indicator of treatment adherence. Also, information on severity of depression was not available.

Conclusions—We did not find a lower suicide risk among people over age 50 who seemingly follow treatment in comparison with those who discontinued treatment with antidepressants at an early stage.

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Contributors

All authors designed and planned the study. AE conducted the literature searches and data management. AE and EA undertook the statistical analysis, and AE wrote the first draft of the manuscript. All authors contributed substantively to the editing of the manuscript and have approved the final version prior to its submission.

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Keywords

Suicide; Antidepressants; Non-Compliance; Aged; Denmark

1. Introduction

Suicide rates in many countries are highest among the middle-aged and older age groups (Erlangsen et al., 2003; Shah, 2007) and depression is one of the strongest predictors for suicide in older people (Conwell et al., 1996; Waern et al., 2003). Treatment with antidepressants is thought to reduce the risk of suicide in depressed older persons (Beyer, 2007; Lebowitz et al., 1997). Over recent years the prescription rates of antidepressants have increased to unprecedented levels (Frey et al., 2000; Grunebaum et al., 2004; Hall et al., 2003; Isacson, 2000; Morgan et al., 2004).

The first stages of antidepressant treatment are associated with high drop-out rates (Bogner et al., 2006). In a recent Danish study as many as 47% of adults aged 50 years and over were found to have discontinued treatment after only one prescription of antidepressants (Erlangsen et al., 2008).

In older people reasons for interrupting treatment are fear of addiction, lack of improvement, not considering depression to be a medical illness, and viewing depression as a normal reaction to adverse events (Givens et al., 2006). Side effects, such as nausea, sexual dysfunction, nervousness, insomnia, loss of appetite (Westenberg et al., 2006), or discontinuation syndrome (Stone et al., 2007; Westenberg et al., 2006) might also lead to early discontinuation. Depending on supplemental payments, costs of the medication might influence decisions about whether to continue treatment as well.

Adults over age 50 in Denmark who were in treatment with antidepressants were found to have 4–6 times higher suicide rates than the general population in the same age range, with rates ranging between 153–273 for men and 69–113 per 100,000 for women (Erlangsen et al., 2008). A regional Canadian study, however, found much lower suicide rates among older recipients of antidepressant (Rahme et al., 2008). A 5-fold higher risk of suicide was found in older adults during their first month of treatment with SSRIs compared to TCAs (Juurink et al., 2006).

We do not know how early discontinuation of treatment with antidepressants affects the suicide risk. Our aim was to compare the suicide risk of adults over age 50 who stopped redeeming antidepressants at an early stage with those who continued. Given that as many as 85–90% of individuals who discontinue treatment are still depressed (Baldwin et al., 2006), we hypothesized that these individuals have a higher risk of suicide than those who seemingly comply with treatment. Also, we wished to assess if persons who previously have been hospitalized for psychiatric disorders are associated with elevated suicide risks.

2. Methods

Data on all persons aged 50 years and older living in Denmark during the period July 1st 1995 to December 31st 2000 were used in the analysis. Individual-level information on antidepressant prescriptions, socio-demographic variables, somatic hospitalizations (between 1980 and 2000), and psychiatric hospitalizations (between 1970 and 2000) were obtained and linked based on the person's unique identification number (Andersen et al., 1999; Eurostat, 1995; Munk-Jørgensen et al., 1997; Pedersen et al., 2006).

The Register of Medicinal Product Statistics records all prescriptions redeemed at pharmacies. In Denmark, antidepressant medications are only available by prescription. Subjects were considered as continuing treatment with antidepressants as long as they kept redeeming prescriptions. Based on the number of pills in the current prescription, we calculated when the next prescription was expected to be filed. A person in ongoing treatment was assumed to consume at least 0.75 pills per day and was allowed to transfer up to 21 'unused' pills from the previous prescription period (to allow for occasional misses and vacation periods). This and a comparable procedure have been recommended and applied in other studies using the same data source (Erlangsen et al., 2008; Hansen et al., 2004; Rosholm et al., 2001).

Early discontinuation was assumed to have occurred when treatment was not continued beyond the first redeemed prescription, i.e. when an individual did not redeem a second prescription of an antidepressant within the expected time frame. Persons who switched to other antidepressants within the treatment phase and continued filing prescriptions with those were considered as continuing treatment.

All persons who commenced a new treatment with antidepressants were included on the date when their first prescription was expected to be replaced by a second prescription (t_0). Persons were censored on the date of the following events: 1) migration, 2) admission to psychiatric hospital (except ambulant care), 3) death, and 4) end of study period. Each individual only entered the study once.

The following time-varying covariates were used for stratification: age, marital status, pension, income, contact with general practitioners, somatic comorbidity measured by the Charlson Index (Charlson et al., 1987), drug type, whether the first psychiatric admission was within the last year or previously, whether admitted for depression, and whether the person was in current ambulatory treatment.

The probability of dying by suicide for the groups continuing and discontinuing treatment was assessed by Kaplan-Meier curves. Unadjusted hazard ratios (Andersen et al., 1993), propensity based hazard ratios (Rosenbaum et al., 1983), and marginal structural models (Robins et al., 2000) were obtained using the SAS software system (SAS system for SunOP, 2003).

3. Results

A total of 230,268 persons aged 50 years and over redeemed a first prescription of antidepressants. Of these, 13,145 were censored prior to the expected date of the second prescription. Among the remaining 217,123 individuals (78,594 men and 138,529 women), 91,374 (42%) subjects did not redeem a second prescription within the expected time frame and were considered as having discontinued treatment early.

In all, 538 persons died by suicide (309 men and 229 women). Men who discontinued treatment early had a suicide rate of 167 per 100,000 compared with a rate of 175 per 100,000 in those who kept on redeeming prescriptions. Their hazard ratio was 0.98 [CI-95%: 0.78–1.23] as shown in Table 1. For women, the rates were 52 and 74 suicides per 100,000 respectively in those who discontinued and continued medication. Women who discontinued treatment early had a hazard ratio of 0.72 [CI-95%: 0.55–0.94]. Other factors associated with elevated suicide risk were a history of previous psychiatric hospitalization, mood disorders, and discontinuation of antidepressants in those in current ambulatory psychiatric treatment.

The rate ratio for men who discontinued treatment was 1.04 [CI-95%: 0.83 – 1.30] in the adjusted regression analysis; for women it was 0.80 [CI-95%: 0.61–1.05]. The marginal structural model showed that early discontinuation of treatment was associated with a rate ratio of 1.12 [CI-95%: 0.89 – 1.39] for men and 0.88 [CI-95%: 0.68 – 1.14] for women. The

corresponding values for the propensity score matched models were 1.04 [CI-95%: 0.83 – 1.30] and 0.80 [CI-95%: 0.61–1.05] for men and women, respectively. None of the included covariates predicted early discontinuation of treatment among those who died by suicide (table not shown).

The probability of surviving (i.e. not of dying by suicide) is shown in Figure 1. For the men aged 50 years and over, little difference was seen in the probability of suicide over time between the two groups. In women, however, those who did not refill a second prescription were less likely to die by suicide (i.e. greater survival) than women who did. When only examining those who had a history of psychiatric hospitalization, discontinuation of treatment was associated with a higher probability of suicide. This applied to both men and women. This finding, however, did not reach statistical significance when adjusting for stratifying covariates in either gender (table not shown).

4. Discussion

This is to our knowledge the first study to assess the suicide risk in people in the second half of life who discontinue treatment with antidepressants.

Both people who continued treatment and those who discontinued treatment early had 3–5 fold higher suicide rates than the general population of the same age range (own calculations; BEF1A, 2007; FOD5, 2007).

Men aged 50 years and over who followed treatment had a 2.3-fold higher suicide rate than women who followed treatment, while men who discontinued treatment had a 3.2 fold higher suicide rate than women over aged 50 in the same situation. In other words, men who discontinued treatment had disproportionately higher suicide rates than women. This could be related to women's more frequent use of primary health care (Vedsted, 2007) and men's higher suicide risk in general (Erlangsen et al., 2003).

People are prescribed antidepressants by their general practitioners for a wide range of disorders (Creed, 2006; Giuliano, 2007; Rahme et al., 2008; Sindrup et al., 1992). Previous psychiatric in-patients and current ambulatory care patients might be more likely to suffer from severe mood disorders. During a psychiatric hospitalization patients are likely to receive a clinical evaluation for depressive symptoms. People with moderate and severe major depression respond better to antidepressant treatment than those with less severe mood disorders (Blazer, 2003). Previous in-patients and current ambulatory care patients who discontinued treatment were found to have slightly higher risks of suicide compared to those who continued treatment. Although this finding was not statistically significant, it seems probable that this group might need the medication and be at higher risk of suicide when interrupting treatment. The survival curves in Figure 1 support this notion.

Individuals with previous psychiatric treatment had a higher risk of suicide than the rest of the study sample. Psychiatric hospitalization is likely to be an indicator of the severity of psychiatric disorder. The lack of specificity associated with risk factors and the low base rate generally hinders the prediction of suicides (Hawton, 1987; Knox et al., 2004; O'Connell et al., 2004). However, general practitioners usually have information on previous hospitalizations and this could be used to intensify follow-up efforts during the initial period of treatment with antidepressants.

As many as 42% of adults over age 50 seemingly interrupted treatment after just one prescription. Discontinuation can be due to lack of medical effect of the drug (Beyer, 2007) or side effects (Westenberg et al., 2006). Nevertheless, evidence-based research suggest that treatment with a single antidepressant or combination of antidepressants, cognitive behavioral

therapy, other types of psychotherapy, and electroconvulsive therapy can reduce depressive symptoms in older adults (Charney et al., 2003; Steinman et al., 2007). Improved adherence to antidepressant treatment has been shown by multimodal interventions focusing on collaborative care (Vergouwen et al., 2003). Furthermore, involvement of case managers who follow and support the treatment course has been linked to lower suicidal ideation (Bruce et al., 2004).

One limitation of our study is the indicator of treatment adherence. We do not know whether pills were actually ingested nor precisely when the treatment was discontinued. Although we controlled for a wide selection of covariates, it would have been preferable to have information on risk modifiers, such as severity of depression, previous suicide attempts, and current psychiatric disorders. Also, having more details regarding the reasons for ending treatment and length of intended treatment would have enabled us to evaluate our findings in more depth. In this regard it is important to acknowledge that, as mentioned above, antidepressants are prescribed for a variety of disorders in adults over age 50.

Underreporting of suicide might be a further limitation, but the registration of suicide in Denmark is generally thought to be reliable (Kolmos et al., 1987). Our findings are not applicable to people who are currently receiving in-hospital treatment.

Advantages of the study include the prospective data collection and longitudinal setting using the entire population for selecting the study sample.

In conclusion, contrary to our expectation, we found no difference in risk of suicide among individuals over age 50 who discontinued treatment with antidepressants at a premature stage in comparison with those who followed treatment.

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Figure 1.

Unadjusted logistic regression assessing the hazard ratios of suicide for persons in continued/discontinued treatment with antidepressants among adults aged 50 years and over living in Denmark during 1995–2000.

	Men			Women				
	Hazard ratio	CI-95%	N Suicide	N No suicide	Hazard ratio	CI-95%	N Suicide	N No suicide
<i>Early discontinuation</i>								
No early discontinuation	1.00		177	45790	1.00		146	79636
Early discontinuation	0.98	[0.78–1.23]	132	32495	0.72	[0.55–0.94]	83	58664
<i>Psychiatric hospitalization</i>								
No early discontinuation	1.00		132	40,347	1.00		98	69,981
-- No previous admission	2.52	[1.79–3.53]	45	5,443	3.56	[2.52–5.02]	48	9,655
<i>Early discontinuation</i>								
-- No previous admission	0.95	[0.73–1.23]	101	30,250	0.70	[0.51–0.97]	58	54,817
-- Previous admission	3.96	[2.68–5.85]	31	2,245	4.43	[2.86–6.88]	25	3,847
<i>Diagnosis during psychiatric hospitalization</i>								
No early discontinuation	1.00		132	40,347	1.00		98	69,981
-- None	3.32	[2.17–5.10]	25	2,094	4.70	[3.11–7.12]	29	4,136
-- Mood disorders	1.93	[1.21–3.09]	20	3,349	2.59	[1.59–4.23]	19	5,519
-- Other disorder								
<i>Early discontinuation</i>								
-- None	0.95	[0.73–1.23]	101	30,250	0.70	[0.51–0.97]	58	54,817
-- Mood disorders	5.39	[3.16–9.19]	15	747	5.84	[3.28–10.42]	13	1,433
-- Other disorder	3.17	[1.89–5.33]	16	1,498	3.52	[1.93–6.41]	12	2,414
<i>Number of psychiatric hospitalizations</i>								
No early discontinuation	1.00		132	40,347	1.00		98	69,981
-- None	2.75	[1.79–4.22]	25	2,877	2.11	[1.20–3.69]	14	4,999
-- 1 previous hospital.	2.27	[1.42–3.64]	20	2,566	4.96	[3.36–7.33]	34	4,656
-- 2+ previous hospital.								
<i>Early discontinuation</i>								
-- None	0.95	[0.73–1.23]	101	30,250	0.70	[0.51–0.97]	58	54,817

	Men			Women				
	Hazard ratio	CI-95%	N Suicide	N No suicide	Hazard ratio	CI-95%	N Suicide	N No suicide
-- 1 previous hospital.	4.22	[2.52–7.10]	16	1,133	3.94	[2.11–7.35]	11	1,973
-- 2+ previous hospital.	3.71	[2.18–6.33]	15	1,112	4.92	[2.81–8.61]	14	1,874
First psychiatric hospitalization								
No early discontinuation								
-- No hospitalization	1.00		132	40,347	1.00		98	69,981
-- more than 1 year prior to t0	2.15	[1.37–3.38]	22	3,054	4.54	[3.12–6.60]	38	5,809
-- less than 1 year prior to t0	3.00	[1.93–4.68]	23	2,389	1.95	[1.02–3.74]	10	3,846
Early discontinuation								
-- No hospitalization	0.95	[0.73–1.23]	101	30,250	0.70	[0.51–0.97]	58	54,817
-- more than 1 year prior to t0	3.61	[2.25–5.77]	20	1,529	4.68	[2.87–7.65]	19	2,706
-- less than 1 year prior to t0	4.81	[2.60–8.89]	11	716	3.80	[1.67–8.66]	6	1,141
Last previous psychiatric hospitalization								
No early discontinuation								
-- No hospitalization	1.00		132	40,347	1.00		98	69,981
-- more than 1 year prior to t0	2.54	[1.47–4.41]	14	1,701	3.98	[2.41–6.58]	18	3,272
-- 1 or less year prior to t0	2.89	[1.66–5.01]	14	1,589	3.16	[1.65–6.05]	10	2,493
-- currently in ambulatory treatment	2.26	[1.36–3.74]	17	2,153	3.44	[2.13–5.57]	20	3,890
Early discontinuation								
-- No hospitalization	0.95	[0.73–1.23]	101	30,250	0.70	[0.51–0.97]	58	54,817
-- more than 1 year prior to t0	2.72	[1.43–5.18]	10	1,018	3.70	[1.93–7.10]	10	1,850
-- 1 or less year prior to t0	5.46	[2.95–10.10]	11	644	4.60	[2.02–10.49]	6	944
-- currently in ambulatory treatment	4.67	[2.45–8.88]	10	583	5.51	[2.78–10.90]	9	1,053
Drug type								
No early discontinuation								
-- TCA	1.00		24	6,792	1.00		29	12,244

	Men			Women		
	Hazard ratio	CI-95%	N Suicide	N No suicide	Hazard ratio	CI-95%
-- SSRI	1.13	[0.73–1.74]	136	34,493	0.83	[0.55–1.25]
-- other types	1.26	[0.68–2.34]	17	4,505	1.03	[0.54–1.95]
Early discontinuation						
-- TCA	0.69	[0.37–1.27]	18	6,667	0.41	[0.21–0.78]
-- SSRI	1.21	[0.77–1.88]	101	22,332	0.70	[0.45–1.09]
-- other types	1.22	[0.62–2.39]	13	3,496	0.65	[0.28–1.47]
Total			309	78,285		
					229	138,300