Discontinuation Rates of Antidepressant Use by Dutch Soldiers

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ABSTRACT Introduction: Soldiers have a higher risk for developing psychiatric disorders that require treatment; often with antidepressants. However, antidepressants as well as the psychiatric disorder, may influence military readiness in several ways. In the general population, early discontinuation of antidepressant treatment is often seen. It is yet unknown whether this occurs to a similar extent in soldiers. The objective of this study was to evaluate discontinuation of antidepressant use by Dutch soldiers in the first 12 months after start and determinants thereof. Materials and Methods: Data were obtained from the military pharmacy. All Dutch soldiers who started using an antidepressant between 2000 and 2014 were included. Kaplan–Meier curves were constructed to estimate the discontinuation rate over time and the influence of each determinant on discontinuation rate was estimated using Cox regression. Results: About 25.9% of de 2479 starters had discontinued their antidepressant use after 1 month; after 3 and 6 months this number increased to 52.7% and 70.3%, respectively. Early discontinuation was higher in soldiers who received their first prescription from a neurologist or rehabilitation specialist (HR 1.85, 95% CI 1.55–2.21, HR 2.66 95% CI 1.97–3.58) compared to soldiers with a first prescription from a general practitioner. In addition, early discontinuation was lower in soldiers who were prescribed serotonin reuptake inhibitors and other antidepressants (HR 0.57, 95% CI 0.51–0.60, HR 0.63, 95% CI 0.55–0.73) and in soldiers between 40 and 50 years of age (HR 0.79, 95% CI 0.70–0.89). Conclusion: More than half of the soldiers discontinued their prescribed antidepressant within 3 months and after 6 months, only 30% were still on antidepressants.

INTRODUCTION

Antidepressants are among the most widely used medications in the general population and are mainly used for the treatment of patients with depressive or anxiety disorders.[1] In a previous study, we have demonstrated that the prevalence of psychotropic medication use by Dutch soldiers may be low in absolute terms (2.5% in 2012) but had increased by approximately 50% compared to 10 years earlier. We also found that antidepressants accounted for almost half of all psychotropic medication use by soldiers.[2] Several studies have indicated that soldiers have a higher risk for developing psychiatric disorders such as post-traumatic stress disorder, depression, generalized anxiety disorder, panic disorder, aggression, and alcohol abuse.[3–9] Antidepressants are considered an important treatment modality for all these disorders.

Adequate treatment of psychiatric disorders is important for soldiers. On one hand, according to Dutch military guidelines, a soldier cannot be deployed when suffering from depression, anxiety, or post-traumatic stress disorder.[10,11] On the other hand, treatment with antidepressants can result in side effects including fatigue, drowsiness, insomnia, blurred vision, and dizziness, which could also make the soldier unfit for deployment.[12–15] Therefore, it is crucial to carefully initiate therapy with antidepressants for soldiers, closely monitor them, and provide adequate guidance and motivational support for the soldier to continue antidepressant intake for a sufficient treatment period.

For depression and anxiety, most guidelines advise continuing treatment with antidepressants for at least 6 months following the disappearance of symptoms.[16,17] However, 30–50% of patients in the general population who commence antidepressant treatment discontinue therapy within 6 months, indicating suboptimal therapy due to misdiagnosis, fear of side effects, lack of effectiveness, or other reasons;[18–21] this suboptimal therapy results in an increased risk of relapse. It is yet unknown whether early discontinuation of antidepressant therapy occurs to a similar extent in soldiers.

We hypothesize that discontinuation rates in soldiers are comparable to the general population. In order to obtain data on discontinuation of antidepressant therapy in soldiers, the objective of this study is to explore the incidence and determinants of the discontinuation of antidepressant use by Dutch soldiers in the first 12 months following start.

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MATERIALS AND METHODS

Setting and Study Population

All Dutch soldiers are treated within the military healthcare system with specialized and obligatory healthcare insurance. All prescription medication is distributed within the military healthcare system through the military pharmacy system.

All drug dispensing data for the complete Dutch military population between January 2000 and March 2015 were obtained from the pharmacy information system of the military pharmacy at the central military hospital in Utrecht. Information about dispensed medication included patient data (anonymized ID, gender, year of birth), type of drug dispensed, dispensing date, number of units dispensed, prescribed daily dose, and prescriber. No informed consent was needed for this anonymized database research.

All soldiers who were first dispensed an antidepressant between January 2000 and March 2014 were included in this study. A starter was identified as a soldier who received a first prescription of an antidepressant between January 2000 and March 2014, which means no prescription for an antidepressant in the 12 months before January 2000. An antidepressant was identified by the Anatomical Therapeutic Chemical (ATC) code, starting with N06A. Patients starting the version of bupropion (Zyban® N06AX12) that is registered for smoking cessation and is prescribed by pulmonologists only were excluded from this study. Persons with psychiatric illness, including antidepressant use, are disallowed from entering the military. Therefore, first dispensing in the dataset was considered to be first use of an antidepressant. The date of the first dispensing of an antidepressant marked the start of the episode, which was referred to as the index date. All starters in this study were followed for 12 months.

Frequency of Discontinuation of Antidepressants

For each included soldier, all prescriptions for antidepressants were identified. The theoretical end date of use of each prescription was calculated using the dispensing date, the number of units dispensed, and the prescribed daily dose. Antidepressant use was considered to be continued as long as there was no gap of more than 60 days between the theoretical end date of a prescription and the start of the subsequent prescription of an antidepressant. Switching to another antidepressant, which is defined as stopping the initial antidepressant and starting a different antidepressant within the N06A ATC-group, was considered to be continuation.

After discontinuation, soldiers were followed for up to 12 months after the index date to identify possible restarts of antidepressant treatment.

Determinants of Discontinuation

For each soldier in the dataset, we identified the following determinants: gender (male/female), age at index date (20–29, 30–39, 40–49, 50–59), type of initial antidepressant dispensed (tricyclic antidepressant N06AA, selective serotonin reuptake inhibitor N06AB, monoamine oxidase inhibitor N06AF and N06AG, other antidepressants N06AX), concomitant use of other psychotropic drugs at baseline (anti-epileptic drugs N03, antipsychotic drugs N05A, benzodiazepines N05B and N05C, psychostimulants N06B), and prescriber specialty (general practitioner, psychiatrist, neurologist, revalidation specialist, other).

Data Analysis

Kaplan–Meier curves were constructed to estimate the frequency of the discontinuation of antidepressant use over time. To identify determinants associated with discontinuation, the determinants were compared for discontinuing soldiers and continuing soldiers using a Cox regression analysis. Data were analyzed using SPSS, version 25.0 (SPSS Inc., Chicago, IL).

RESULTS

The total number of Dutch soldiers varied from 29,257 (5.73% female) to 50,265 (8.72% female) between 2000 and 2014. Almost two-thirds of the population was below 40 years of age. The population age distribution indicated two peaks; one at the age of 20–25, and one at the age of 40–45, which was consistent during the study period.

Two thousand four hundred and seventy-nine (2479) soldiers who started antidepressant treatment between January 2000 and March 2014 were identified. The frequency of soldiers that started an antidepressant varied between 0.45% in 2000 to 0.58% in 2013 (full last calendar year). Of the patients, 81.6% were male, and the average age at start was 36.5 years (men 37.9 and women 30.1). Serotonin reuptake inhibitors were dispensed to 62.8% of the antidepressant starters, and almost half of the antidepressants were initiated by a general practitioner (46.3%). A total of 220 patients (8.9%) used one or more other psychotropic drugs at the moment of starting the antidepressant, especially benzodiazepines (4.8%), psychostimulants (2.5%) and anti-epileptic drugs (1.4%). Table I depicts the characteristics of the starters of antidepressants between January 2000 and March 2014.

Of the patients, 40.6% (1007 patients) only filled one prescription, and the mean duration of the first prescription was 46.6 days. During the follow-up period, 8.1% (200 patients) switched their antidepressant.

After the first month, 25.9% ($N = 643$) of the starters had discontinued their antidepressant use. After 3 and 6 months, this number increased to 52.7% ($N = 1306$) and 70.3% ($N = 1743$) respectively (Fig. 1). After 1 year, 87.4% of the starters had discontinued their antidepressant use. In the present study we identified first prescribers only, this tells us something about the specialism of the doctor who initiated antidepressant treatment and at our best guess could tell us something about the indication. Tricyclic antidepressants are

known to be prescribed for more indications than depressions or anxiety only. Therefore a sensitivity analysis was done. This analysis without the tricyclic antidepressant (N = 2068) indicated that after the first month, 23.0% (N = 475) of the starters had discontinued their antidepressant use; after 3 and 6 months, this number increased equally to 48.6% (N = 1007) and 67.2% (N = 1390) respectively (data not shown).

TABLE I. Characteristics of Starters of Antidepressants Between 2000 and 2014 (N = 2,479)

Characteristics	N = 2,479	
	N	%
Sex		
Male	2,023	81.6
Female	456	18.4
Age		
20–30	789	31.8
30–40	660	26.6
40–50	614	24.8
50–60	416	16.8
Type of initial antidepressant		
Tricyclic antidepressants (TCA)	411	16.6
Selective serotonin reuptake inhibitors (SSRI)	1557	62.8
MAO inhibitors (MAOi)	2	0.1
Other antidepressants	509	20.5
Concomitant use of psychotropic drugs at baseline		
Anti-epileptic drugs	35	1.4
Antipsychotic drugs	18	0.7
Benzodiazepines	118	4.8
Psychostimulants	63	2.5
Prescriber		
General practitioner	1147	46.3
Psychiatrist	979	39.5
Neurologist	150	6.1
Rehabilitation specialist	47	1.9
Other	156	6.3

There was no difference in discontinuation between men and women (Hazard Ratio (HR) 1.01, 95% CI 0.90–1.12). The mean continuation time for both groups was 137 days. The soldiers between 40 and 50 years (mean continuation time of 152 days) were less likely to discontinue their antidepressants early than soldiers between 20–30 years (reference age group mean continuation time of 126 days) (HR 0.79, 95% CI 0.70–0.89, Fig. 2). Early discontinuation was lower in soldiers who were prescribed serotonin reuptake inhibitors (mean continuation time 151 days) and "other antidepressants" (mean continuation time 136 days) than soldiers who were prescribed tricyclic antidepressants (TCAs) (mean continuation time 89 days) (HR 0.57, 95% CI 0.51–0.60, HR 0.63, 95% CI 0.55–0.73 respectively, Fig. 3).

The concomitant use of other psychotropic medication at baseline did not influence discontinuation rates (Table II). Soldiers who had their antidepressants initially prescribed by a psychiatrist (mean continuation time 157 days) had lower discontinuation rates than soldiers who had their antidepressants initially prescribed by a general practitioner (mean continuation time 135 days) (HR 0.84 95% CI 0.77–0.92). On the other hand, when the antidepressant was initially prescribed by a neurologist (mean continuation time 73 days) or rehabilitation specialist (mean continuation time 55 days), discontinuation rates were higher (HR 1.85, 95% CI 1.55–2.21, HR 2.66, 95% CI 1.97–3.58, Fig. 4).

In this study, 17.5% (434) of the patients that had discontinued antidepressant use restarted their therapy before the end of the follow-up period. To elaborate, 19.8% (N = 127) of the patients who stopped within the first 30 d and 21.9% (N = 381) of the patients who stopped within the first

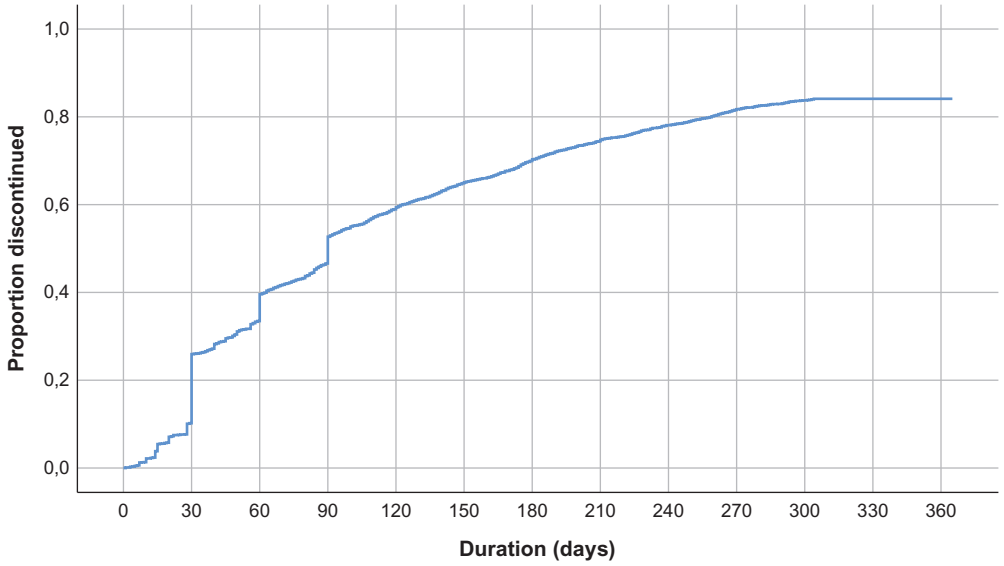

FIGURE 1. Proportion of discontinuers of antidepressant use (N = 2,479).

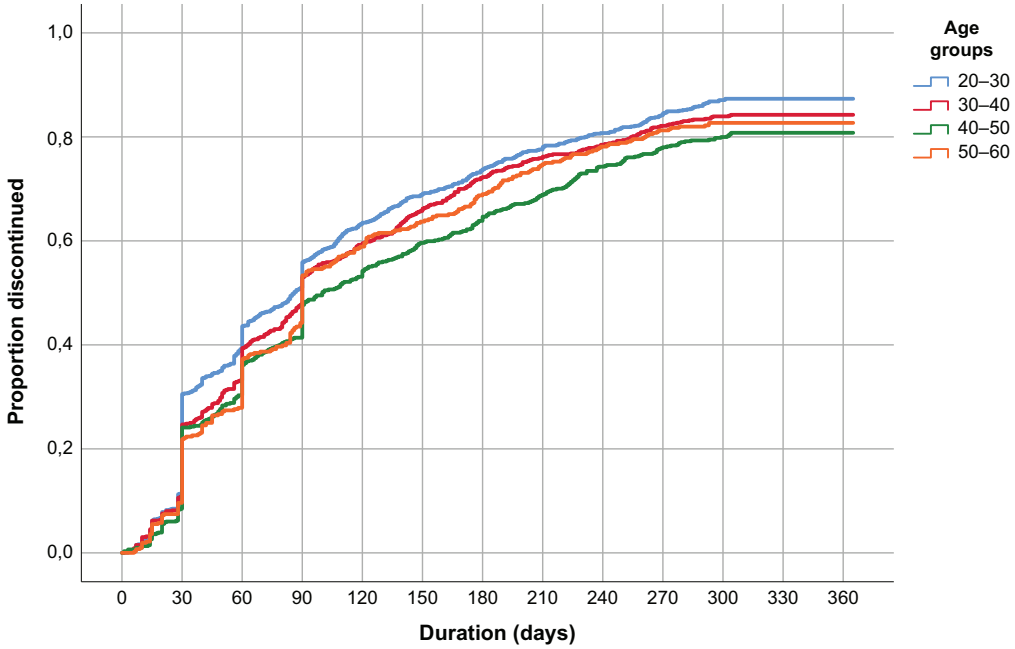

FIGURE 2. Proportion of discontinuers of antidepressants for different age groups.

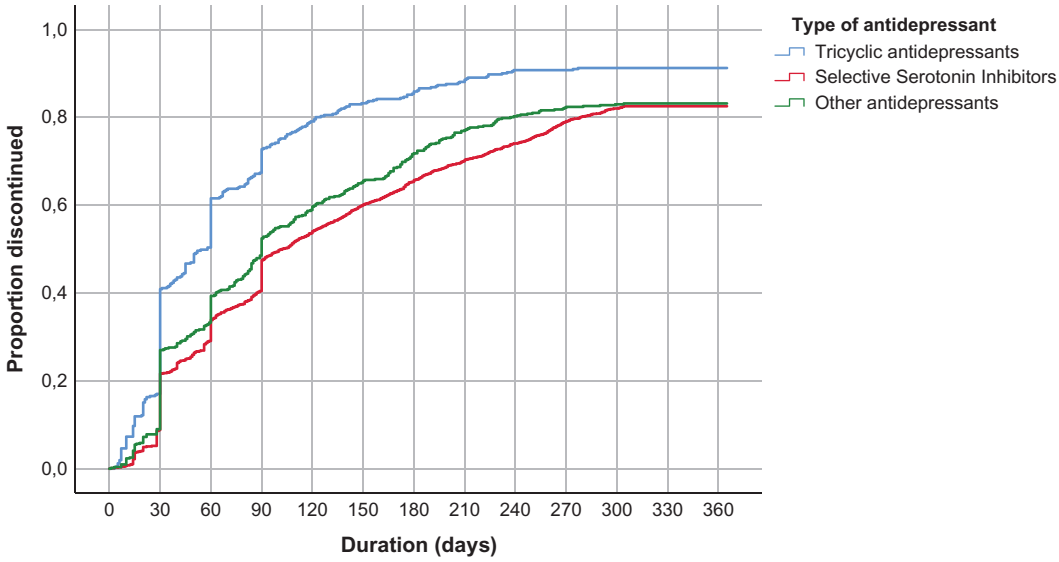

FIGURE 3. Proportion of discontinuers of antidepressants for different types of antidepressants.

6 months restarted antidepressant use before the end of the 12 month follow-up period.

DISCUSSION

This study demonstrates a high rate of early discontinuation of antidepressant use by Dutch soldiers. Within a month, a quarter of those that started antidepressant treatment had already stopped, and after 6 months, only 30% still were treated.

In the general population, discontinuation rates are also high (30% to 50% in the first 6 months),[18–20,22] and the rates of early discontinuation in this study on Dutch soldiers was even higher. Such statistics are problematic for several reasons. First, guidelines for the treatment of depression and anxiety advise the continuation of treatment with antidepressants for at least 6 months following disappearance of symptoms.[16,17] Second, early discontinuation of antidepressant treatment results in higher relapse rates compared with treatment continuation.[23] Third, a soldier in relapse for different psychiatric disorders is unfit for deployment. Therefore, early discontinuation can decrease readiness and deployment rates.

In this study, the soldiers had already consulted a military healthcare professional and collected the medication at the military pharmacy. Hence, they already overcame several barriers to care. Still, after that up to 70.3% of these soldiers did not meet the recommended 6 months of treatment after disappearance of the symptoms, risking relapse and longer treatment. These soldiers risked being unfit for deployment again and possibly for a longer period of time.

TABLE II. Hazard Ratios on Discontinuation for Different Determinants of Starters of Antidepressants Between 2000 and 2014 (N = 2479, 95% CI = 95% Confidence Interval, Ref=Reference)

Characteristics (N = 2479)	Hazard Ratio	95% CI
Sex		
Male	Ref	Ref
Female	1.01	0.90–1.12
Age		
20–30	Ref	Ref
30–40	0.91	0.81–1.02
40–50	0.79	0.70–0.89
50–60	0.86	0.75–0.98
Type of initial antidepressant		
Tricyclic antidepressants (TCA)	Ref	Ref
Selective serotonin reuptake inhibitors (SSRI)	0.57	0.51–0.64
Other antidepressants	0.63	0.55–0.73
Concomitant use of psychotropic drugs at baseline		
None	Ref	Ref
Anti-epileptic drugs	1.17	0.81–1.67
Antipsychotic drugs	0.90	0.55–1.47
Benzodiazepines (one)	0.76	0.60–0.96
Benzodiazepines (two)	0.77	0.45–1.33
Psychostimulants	0.77	0.58–1.03
Prescriber		
General practitioner	Ref	Ref
Psychiatrist	0.84	0.77–0.92
Neurologist	1.85	1.55–2.21
Rehabilitation specialist	2.66	1.97–3.58
Other	1.18	0.99–1.41

There are several factors that can contribute to early discontinuation. First, several studies describe stigma-related barriers that soldiers must overcome before seeking help for their mental health problem. Soldiers have a different attitude to mental illness than the general population. Soldiers are more positive then civilians about the causes of mental illness but are more negative about the rights to employment for those with mental illness.[24–28] Although the soldiers in this study already overcame some of these stigma-related barriers by coming to a military healthcare professional, stigma may still have contributed to early discontinuation.

Second, it is possible that the patients experienced lack of effectiveness, side effects, or feared for side effects, resulting in early discontinuation.[18,21] Third, it is possible that the prescriber or pharmacist did not provide enough information about the effects of the antidepressant, leaving the soldiers with wrong expectations. This could result in the disappointment of the soldier and the early discontinuation of the antidepressant.[18,21,29]

A more speculative explanation could be that psychiatric problems are more severe in soldiers. This speculation envisions the soldier to be struggling with their psychiatric disorder for a longer period of time, maybe even years, before consulting a healthcare professional. Therefore, the psychiatric disorder may have been evolved over time and may be more complicated. Treatment success rates may be lower in this case and treatment is stopped early due to lack of results.

The general assumption in this study was that discontinuing antidepressant treatment before 6 months of use was

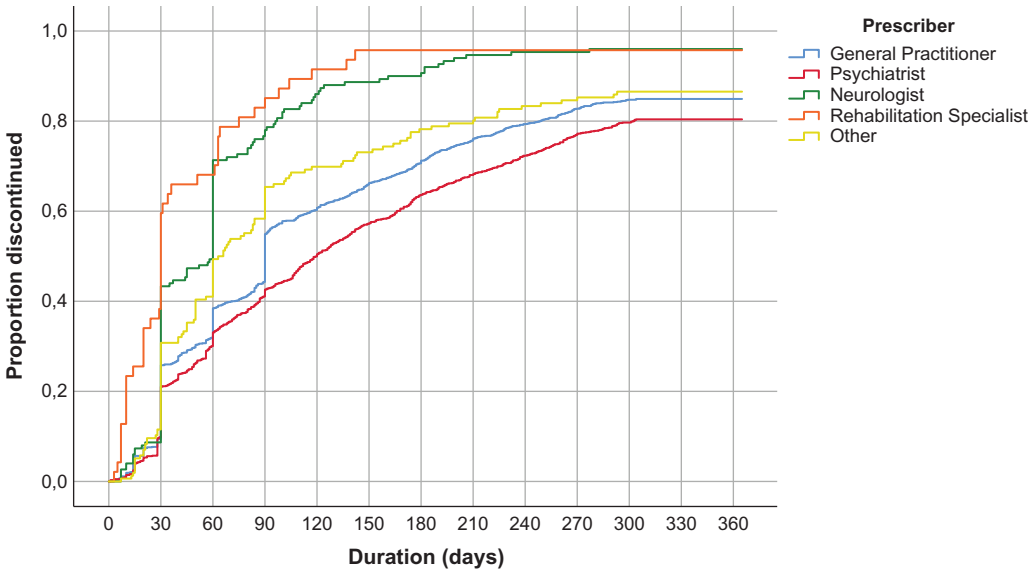

FIGURE 4. Proportion of discontinuers of antidepressants for different first prescribers.

considered early discontinuation. This assumption is based on treatment guidelines for depressive disorders or general anxiety that state that treatment should be continued for at least 6 months following disappearing of symptoms. However, although antidepressants are most often prescribed for psychiatric disorders, they can also be prescribed for other disorders, including neuropathic pain. Often, when neurologists or rehabilitation specialists prescribe TCAs, the indication is neuropathic pain, and some of the TCAs prescribed by the general practitioner were also likely meant to treat this other indication. We did find a higher discontinuation rate in users of TCAs compared to other antidepressants. However, when all patients treated with TCAs were excluded from the analysis, the overall discontinuation rates remained high.

It could also be possible that prescribers meant to prescribe antidepressants for a short-term treatment for other reasons, and that early discontinuation does not reflect nonadherence with guidelines, but rather a deliberate clinical decision. However, we discussed with several prescribers within the military possible intentional shorter use of antidepressants. All prescribers declared that there is no indication for which the intended treatment duration with antidepressants is shorter than 6 months after disappearance of the symptoms following treatment guidelines. One prescriber mentioned antidepressant use for smoking cessation, but use of bupropion, registered for smoking cessation therapy, was excluded from the dataset.

A further limitation of this study is that it is in theory possible, although forbidden, for soldiers to go outside the military healthcare system to keep their psychiatric indication or therapy hidden from their employer. However, soldiers in our population already took the step to be diagnosed and treated in military psychiatry and are less likely to go to another pharmacy because their treatment is already registered.

This study also has several strengths, the most important of which is that this study includes the antidepressant use of the entire Dutch military population for more than a decade. Also, this study reveals antidepressant usage patterns in the military population with access to routine clinical care over the years.

Overall, the number of early discontinuers in Dutch soldiers is high and is much higher than in the general population. This early discontinuation is problematic for soldiers because it may negatively influence the treatment success, both on short term and long-term. It may directly influence readiness for deployment. But also, the impact of underlying mental health problems and the side effects of antidepressants both lead to occupational ineffectiveness, prolonged retention, decreased productivity of soldiers and increase social exclusion for those who leave the armed forces.

Further research on this topic should be focused on the reasons why early discontinuation of antidepressants is so frequent, how full compliance and early discontinuation are related to treatment outcomes as well as occupational and deployment readiness and how to improve antidepressant treatment for our military. Ultimately, further research can add to the knowledge and confidence of commanders that soldiers with psychiatric disorders will receive the full course of optimal treatment and will be ready for deployment when on the job.

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