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Influence of antidepressant therapy on sick leave in primary care: ADAS, a comparative observational study

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Abstract

Background: Compared to other European countries, Sweden's yearly sick leave expenditures are moderate. Common mental disorders (CMD) are important causes of sick leave, affecting 10−15% of the adult population. A Swedish register based study indicates that antidepressant therapy for patients on long-term sick leave for CMD leads to longer sick leave and higher frequency of non-time-limited sickness compensation as compared to psychotherapy, work oriented rehabilitation, and other therapies.

Aim: To verify if patients on antidepressant therapy and on long-term sick leave for depression, anxiety and stress-related mental disorders have a longer sick leave than patients treated with other therapies.

Method: Prospective, observational study at 28 primary health care centers in the Region Västra Götaland, Sweden, including 192 patients on sick leave for CMD. Outcome measures were gross and net sick leave days.

Interpretation: There were no significant differences in sick leave days (gross or net) due to CMD when comparing the patients treated and not treated with antidepressants during the 12 month observation period. The groups differed at baseline only concerning frequency of exhaustion disorder, with a higher frequency of exhaustion disorder in the group without antidepressants. Analysis of other possible factors associated with shorter or longer sick leave only showed associations with the patient's own perception of possibility of returning to work in near and distant future. An important factor associated with longer sick leave was the patient's own perception of possibility of return to present workplace. As CMD are important causes of sick leave and sick leave costs, this factor should be highlighted in future research on the rehabilitation process.

Keywords: Epidemiology, Public health, Psychiatry

1. Background

Compared to other European countries, Sweden's yearly sick leave expenditures are moderate, i.e. neither high nor low [1]. Depression, anxiety syndromes and stress related mental disorder, often referred to as Common Mental Disorders (CMD), are some of the main causes of disability, affecting $10-15\%$ of the adult Swedish population [2, 3]. An increase in depressive symptoms has been reported among the younger population [4, 5]. Depression and anxiety are common but often hidden problems among patients seeking primary health care (PHC), and co-morbidity with chronic illnesses is frequent [6]. According to epidemiological studies, about 70% of patients with depression and anxiety are treated in PHC, and about 75% of all anti-depressants are prescribed by general practitioners (GPs) [6]. Most of the patients have disabilities (mild, moderate or severe) that are not always proportionate to the degree of depression [7]. At most workplaces there are increasing demands on cognitive performance. CMD influence the cognitive performance and frequently cause sick leave for both sexes, albeit more common among women. In 2014 depression was the main diagnosis in about 35% of all cases of prolonged sick leave (≥ 60 days) [8]. Swedish national guidelines for depression and anxiety recommend cognitive behavioral therapy (CBT) as the first treatment for mild to moderate depression as well as for panic and social anxiety disorders [9]. The availability of psychologists and psychotherapists in PHC is limited, and the need for psychological therapy is not adequately met. As a result of this and in combination with previous good experience from antidepressant therapy, antidepressant medication is frequently prescribed [10]. Antidepressants have been shown to be effective for major depression and for

several anxiety disorders [11]. Additional alternative forms of treatment are physical therapy, early medical return visits, or a combination of antidepressants and psychological therapy.

Prescription of antidepressants, especially SSRIs, is relatively high in Sweden. Among adults, more than 12% of females and 6% of males were in 2015 on treatment with antidepressants [12].

Few studies in the area of depression and anxiety have examined the effect of treatment in terms of function, work ability or return to work (RTW). Thus, there is strong scientific evidence that antidepressants and psychological therapy have beneficial effects on depressive and anxiety symptoms, but there is little support that this results in an earlier RTW [13]. Studies that have evaluated the effects of these measures in the PHC also show that good effects on depressive and/or anxiety symptoms do not automatically lead to an earlier RTW, or improved job performance [7, 9, 14, 15]. There are few studies evaluating the results in terms of job performance [13]. The outcome of treatment of depression and/or anxiety may not be directly associated with earlier RTW, as this is determined by several factors aside from the mental state. These would include, for example, the individual's work ability and also environmental factors of social and economic nature, not least the current labor market. In their literature review, Neuwenhausen et al [13] found that interventions that included work place contact or cognitive behavioral therapy had moderate quality evidence of earlier return to work. In a recent Swedish register study, a significant finding was that patients receiving antidepressants had longer sick leave [16]. The Swedish register study showed that patients treated with antidepressants for psychiatric diagnosis (mostly anxiety, depression and stress-related disorder) were at greater risk for longer sick leave or indefinite sick leave than those who received psychotherapy, work oriented rehabilitation or alternative treatment [16]. In the study it was not possible to determine whether patients treated with antidepressants constituted a different group compared to those who received psychological or other treatment. The study could not distinguish between different diagnostic groups, severity of symptoms (mild, moderate or severe) or concurrent co-morbidity, because it was based on records and retrospective questionnaires. The authors stated that in-depth studies of the effect of pharmacological and other therapies in the treatment of mental illness should be implemented [16]. As antidepressant pharmacological therapy is very frequent in primary care, and a great part of sick leave reporting is conducted in primary care, we initiated the present study to determine whether the Swedish register study finding is relevant for CMD patients in primary care. The hypothesis was that antidepressant therapy means longer sick leave than other treatment in primary care for patients with mild to moderate depression, anxiety syndrome, or stress-related mental illness. The rationale for longer sick leave when on antidepressants could be their passivating effect, i.e. a known side effect of antidepressants, thus counteracting other activating, therapeutic measurements for patients [17].

1.2. Aim

To verify if patients on antidepressant therapy and on long-term sick leave for mild and moderate depression, anxiety syndrome and stress-related mental disorders have a longer sick leave than patients treated with psychological and other therapies.

2. Method

The study Antidepressants in Depression, Anxiety syndrome and Stress-related mental disorders (ADAS study) was conducted as a prospective observational study in Region Västra Götaland, Sweden among primary care patients on sick leave ≥ 14 days with the diagnoses mild to moderate depression, anxiety, or stress-related mental illness. The participants were followed during 12 months and followed up in terms of sickness, psychological therapy, drugs, return to work, self-rated health, function, lifestyle, and other diseases and disorders.

2.1. Population

Persons 18- 60 years old, residing in Region Västra Götaland region, attending primary care, and willing to participate took part in the study. They must have had a minimum of 50% employment at inclusion and been on sick leave ≥ 14 days due to depression, anxiety, or stress-related mental illness. Persons studying full time or unemployed persons engaged in employment agency proceedings were also included as they were also eligible for sick leave. Concerning sick-listing the conditions for these two groups are the same as for anyone at work in Sweden. At the assessment interview they had to meet the criteria for mild to moderate depression, anxiety, or stress-related mental illness according to Mini International Interview (M.I.N.I.) [18]. Exhaustion disorder was diagnosed according to a review of the diagnostic criteria for the condition. All forms of physical and psychiatric concurrent problems or diagnoses were accepted if not listed among exclusion criteria. All forms of pharmacologic therapy could be used. Exclusion criteria were the following: persons with schizophrenia, addiction or substance dependence, psychosis, bipolar disorder, high risk of suicide, ongoing severe depression, generalized anxiety disorder, and persons who did not understand or speak Swedish sufficiently.

2.2. Recruitment and structured clinical interview for diagnosis

Twenty-eight primary health care centers (PHCC) in Region Västra Götaland region agreed to participate in the recruitment of study participants. The rehabilitation coordinator (RC) at the PHCC searched for potential participants through the IT reporting tool MedRAVE (Medrave Software AB │ contact@medrave.com) around every other week. The first selection by the rehabilitation coordinator was based on age,

sick leave duration ($\geq$14 days), and diagnosis concerning application for sickness benefit. The ICD-10 diagnoses were F32, F33, F34, F38, F39, F41, F43, F48, or F99 (excluding severe depression and generalized anxiety disorder). The rehabilitation coordinator sent an information letter to potential participants by mail with an inquiry about whether the patient was interested in participation in the study and whether the study nurse could make contact. Only if the individual agreed to participate was information about the participant forwarded to the study nurse, who then made an appointment for interview and further information.

The interview took place at the PHCC. The research nurse provided written and oral information about the study, with the opportunity to ask questions, and carried out a diagnostic interview. During the interview, a structured clinical interview with the M.I.N.I. and a review of the diagnostic criteria for exhaustion disorder were used [18, 19]. At the clinical assessment inclusion and exclusion criteria were considered. A total of 192 persons were included, see flow chart Fig. 1.

2.3. Data sources

At inclusion, information on background variables, depressive and anxiety symptoms, and perceived work ability was collected by validated self-assessment instruments. Data concerning days on sick leave as well as data concerning all baseline variables were also collected at 3, 6, and 12 months. Self-rated numbers of short-term sick leave days were also collected.

The following validated and standardized scales regarding self-rated health and functioning were used at baseline and at follow-up at 3, 6, and 12 months: 1) Work Ability Index (WAI): Self-rated work ability - human resources in relation to health demands at work [20], 2) Montgomery Asberg Depression Rating Scale - Self Assessment (MADRS-S): depressive symptoms [21], 3) Karolinska Exhaustion Disorder Scale (KEDS): fatigue symptoms [22], 4) Hospital Anxiety and Depression Scale, HADS: degree of anxiety and depression [23], 5) Work and Social Adjustment Scale (WSAS): self-rated functional level [24], 6) Alcohol Use Disorders Identification Test (AUDIT): alcohol use [25], 7) Satisfaction with life scale (SWLS) [26], 8) EQ-5D: health-related quality of life [27], and exhaustion disorder [28].

The participants specified prescribed and actually taken antidepressants and other therapies at baseline, and at follow-up at 3, 6, and 12 months. In addition, self-reported sick leave less than a week, not requiring a medical certificate in Sweden, was also reported.

2.4. Statistical methods

Standard statistical methods were used for descriptive statistics. Continuous variables were analyzed by independent-samples t-test or Mann-Whitney U test (nonparametric data) and categorical variables or frequencies by Pearson chi-square
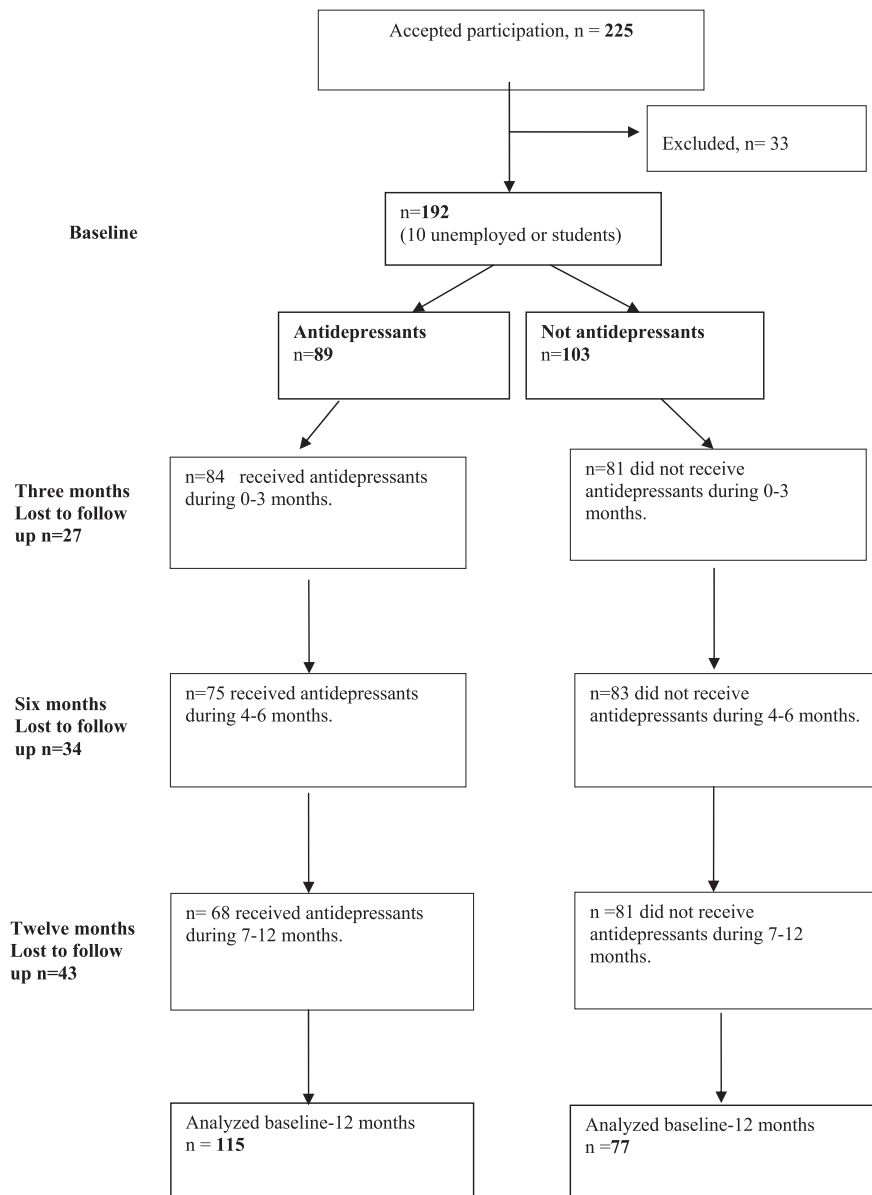
Fig. 1. Number of patients treated with/not treated with antidepressants at 3, 6, and 12 months. Shown at the bottom, the number analyzed in each group during 12 months (115 with antidepressants and 77 without antidepressants). The difference between the groups was treatment or not treatment with antidepressants during any period from baseline to 12 months. Both groups could receive psychological, physical, and other treatments as usual. At three, six and twelve months different proportions were treated with antidepressants.

test. As none of the continuous variables were fully normally distributed, we used both tests to ensure that the results were robust. The same results were obtained in both tests. Associations between antidepressant therapy and sick leave/return to work were tested using logistic regression analysis and presented as odds ratios with 95% Confidence Intervals (CI). The analysis was controlled for age, sex, and socioeconomic status. The statistical analyses were made using statistical software SPSS, version 24. Statistical significance was set at $p < 0.05$.

2.5. Power analysis

Assumption was based on an approximate measure obtained through a registry-based study [16]. With a power of 0.80 and significance level of 0.05% (alpha = 0.05 and beta = 0.20), 168 individuals were required for analysis, also taking into account sex, socio-economic, and environmental factors at work. The required number to be included was set at 180 to allow for participants lost to follow-up.

2.6. Ethical approval

Approved by the ethical committee in Gothenburg, Sweden (577-13, 2013-11-18).

3. Results

Starting in January 2014, 225 patients on sick leave were recruited from 28 PHCCs during one year in Region Västra Götaland. The participants underwent a diagnostic interview at the PHCC. Thirty three patients did not fulfill the diagnostic CMD criteria specified for the study, see Fig. 1. Participants who at any time during the study period were treated with antidepressants were identified as the antidepressant group, whereas participants who were never treated with antidepressants during the study period were identified as the "not antidepressant" group. Other treatment such as psychological treatment, physical activity, and other could be present in the two groups. Some participants were lost to follow up: 27 at three months, 34 at six months and 43 at 12 months (Fig. 1). Ten of the patients on sick leave were studying or unemployed engaged in employment agency proceedings, with equal allocation in the groups with and without antidepressants. Data from all patients concerning medication and sick leave were collected from the electronic records.

At baseline the frequency of depression, post-traumatic stress syndrome (PTSD), and anxiety syndrome was equivalent between the groups, whereas there was a significant difference concerning exhaustion disorder, p = 0.006, see Table 1.

In number and percentage, 11 (6%) of the participants did not fulfill depression disorder according to M.I.N.I, 179 (93%) did not have PTSD, 78 (41%) did not fulfill anxiety syndrome according to M.I.N.I., and 30 (16%) did not have symptoms of at least minor exhaustion disorder. Regarding demographics, there were no statistically significant differences between the groups, see Table 2. There were also no statistically significant differences concerning other chronic disease symptoms.

Concerning current visits to primary health care, a significantly higher proportion of the patients treated with antidepressants met the GPs compared to those not treated with antidepressants, p = 0.010, see Table 3.

Table 1. Psychiatric diagnoses for patients at base-line treated and not treated with antidepressants, number and percentage. Exhaustion disorder was diagnosed according to a review of the diagnostic criteria for the condition [18].

	Total	Antidepressants	Not antidepressants	p
Depression (Mini)	181 (94)	86 (47·5)	95 (52·5)	0·40
PTSD (Mini)	13 (7)	5 (38·5)	8 (61·5)	0·43
Anxiety syndrome (Mini)	114 (59)	60 (52·6)	54 (47·4)	0·44
Exhaustion disorder	158 (84)	67 (42·4)	91 (57·6)	0·006

Table 2. Demographics at baseline for patients with and without antidepressants during the observation period 0−12 months, respectively, as well for the total group. Figures indicate numbers and percentage (%) of patients or means and standard deviation (SD). Ten persons out of the 192 were unemployed or students.

	Antidepressants n = 89	Not antidepressants n = 103	Total n = 192	p
Age				
Mean (SD)	42·9 (11·1)	42·5 (9·1)	42·7 (10)	0·78
Gender				
Male	18 (20)	23 (22)	41 (21)	0·72
Female	71 (80)	80 (78)	151 (79)	
Marital status				
Married or cohabiting	64 (72)	78 (76)	142 (74)	0·55
single	25 (28)	25 (24)	50 (26)	
Cohabiting with children <18 years				
Yes	43 (48)	61 (59)	104 (54)	0·13
No	46 (52)	42 (41)	88 (46)	
Education				
Junior high school	6 (7)	6 (5·8)	12 (6)	0·60
Senior high school	48 (54)	49 (47·6)	97 (51)	
University	35 (39)	48 (46·6)	83 (43)	
Born outside the Nordic countries				
Yes	9 (10)	16 (15·5)	25 (13)	0·28
No	79 (90)	87 (84·5)	166 (87)	
Smoking				
Yes	24 (27)	19 (18)	43 (22)	0·16
No	65 (73)	84 (82)	149 (78)	
SEI				
Senior office worker	30 (36·6)	47 (51)	77 (44)	0·12
Lower office worker	17 (20·7)	19 (20)	36 (21)	
Worker or student	35 (42·7)	27 (29)	62 (35)	

Table 2. (*Continued*)

	Antidepressants n = 89	Not antidepressants n = 103	Total n = 192	p
Leisure-time physical activity				
Never	15 (17)	15 (15)	30 (16)	
At least 4 h per week	74 (83)	87 (85)	161 (84)	0·68
Sick leave at present				
Yes	79 (90)	90 (87)	169 (88·5)	0·61
No	9 (10)	13 (13)	22 (11·5)	
MADRS	n = 88	n = 102		
Mean (SD)	21·0 (8·3)	20·32 (8·0)	20·6 (8·1)	0·58
BDI	n = 87	n = 100		
Mean (SD)	23·6 (10·4)	23·1 (9·1)	23·3 (9·7)	0·71
WAI 87/103	n = 87	n = 1033		
Mean (SD)	3·3 (2·7)	2 (2·7)	3·2 (2·7)	0·82
HAD anxiety	n = 87	n = 103		
Mean (SD)	10·8 (4·1)	10·7 (4·1)	10·8 (4·1)	0·93
HAD depression	n = 88	n = 103		
Mean (SD)	8·6 (4·4)	8·72 (4·3)	8·7 (4·4)	0·84
WSAS	n = 86	n = 102		
Mean (SD)	23·8 (8·5)	22·8 (8·2)	23·2 (8·4)	0·4
Audit	n = 78	n = 89		
Mean (SD)	4·1 (5·0)	3·6 (3·4)	3·9 (4·2)	0·46
EQ5D	n = 89	n = 103		
Mean (SD)	0·53 (0·30)	0·56 (0·28)	0·55 (0·29)	0·55
SWLS	n = 86	n = 102		
Mean (SD)	19·0 (6·4)	20·4 (6·4)	19·8 (6·4)	0·13

Table 3. Frequencies of care visits and contacts completed by 12 months for patients treated with antidepressants and not treated with antidepressants.

Number of contacts during 12 months	Total	Antidepressants n (%)	Not antidepressants n (%)	p
GP or company doctor	163	99 (61)	64 (39)	0·010
Physiotherapist and physical training	79	46 (58)	33 (42)	0·24
Counselor, psychologist, psychiatrist	147	84 (57)	63 (43)	0·.13
Other MD specialists	49	30 (61)	19 (39)	0·22
Other	58	32 (55)	26 (45)	0·62

There were no statistically significant differences concerning short duration of sick leave (sick leave 0–30 days) and long duration of sick leave (>30 days) between the group of patients who received antidepressants and the group of patients who did not receive antidepressants during the 12 months follow-up. The results were relevant for both gross and net sick leave.

To study factors potentially associated with shorter or longer sick leave duration other than antidepressant therapy, odds ratios were examined for associations between sick leave duration (0–30/>30 days during 12 months) and socio-economic status, marital status, physical activity level, psychotherapeutic treatment, and the individual's own judged work ability in present job at inclusion, controlled for antidepressant therapy, sex, and age. There was a statistically significant difference concerning net sick leave days (≤30/>30) between those patients who judged their own work ability in present job within two years as "probable" compared with those patients who judged themselves as having "non-work ability" in present job within two years: OR (95% CI) = 2.3 (1.1–5.0), i.e. patients who received longer sick leave during the 12 months follow up judged their own work ability within two years more negatively. Likewise, patients who reported a motivation to work at the same job in the next year had significantly fewer gross and net sick leave days: OR 4.5 (1.2–17.0) and 6.1 (2.2–16.7), respectively, indicating that patients with longer sick leave were more negative towards working at the same job in the next year, see Table 4.

4. Discussion

In this observational study of patients in primary care on sick leave due to CMD, there were no significant differences in sick leave duration when comparing the patients treated with antidepressants and those not treated by antidepressants during the 12 month study period. The groups differed concerning the frequency of presence of exhaustion disorder at baseline, with a higher frequency of individuals with exhaustion disorder in the group without antidepressants; otherwise, there were no differences between the groups. All demographic, lifestyle, and symptom scores monitored at baseline were similar in both groups. Analysis of other possible factors associated with shorter or longer sick leave only showed association with the patient's own perception of possibility of return to work in the near and distant future, i.e. within two years.

The strengths of the study were the prospective design and that it was carried out in the primary care context, where the absolute majority of CMD treatment is conducted and sick leave certification is done. More than 75 % of all prescriptions of SSRI and other antidepressants are given in primary care, and around 70 % of all patients with CMD are taken care of solely in primary care [6]. Another strength was the long

Table 4. Odds ratios for differences in gross sick leave and net sick leave days concerning possible explanatory variables controlled for age, sex, and antidepressant therapy.

Variables			0−30 days n (%)	>30 days n (%)	OR (95% CI)	P
Socioeconomic division (SEI)	High	Gross sick leave	8 (42)	59 (44)	0·88 (0·33−2·49)	0·80
	Low	days	11 (58)	75 (56)		
	High	Net sick leave	16 (42)	51 (44)	0·84 (0·39−1·8)	0·65
	Low	days	22 (58)	64 (56)		
Marital status	Live together	Gross sick leave days	14 (74)	101 (69)	1·2 (0·41−3·7)	0·72
	single		5 (26)	46 (31)		
	Live together	Net sick leave days	28 (70)	87 (69)	1·0 (0·45−2·2)	1·0
	single		12 (30)	39 (31)		
Physical activity	At least 4 h/w	Gross sick leave	14 (70)	110 (74)	0·83 (0·29−2·4)	0·74
	Never	days	6 (30)	38 (26)		
	At least 4 h/w	Net sick leave days	28 (68)	96 (76)	0·62 (0·27−1·4)	0·25
	Never		13 (32)	31 (24)		
Psychotherapy during 3-12 months	Yes	Gross sick leave	11 (61)	85 (61)	1·3 (0·44−3·6)	0·65
	No	days	7 (39)	54 (39)		
	Yes	Net sick leave days	23 (61)	73 (61)	1·3 (0·58−2·8)	0·55
	No		15 (40)	46 (39)		
Own judged work ability in present job even within two years	Probably	Gross sick leave	13 (65)	75 (52)	1·7 (0·64−4·7)	0·29
	Probably not	days	7 (35)	70 (48)		
	Probably	Net sick leave days	28 (68)	60 (48)	2·3 (1·1−5·0)	0·030
	Probably not		13 (32)	64 (52)		
Motivated to work at the same job in the next year	Yes	Gross sick leave	14 (82)	76 (56)	4·5 (1·2−17·0)	0·028
	No	days	3 (18)	61 (45)		
	Yes	Net sick leave	30 (83)	60 (51)	6·1 (2·2−16·7)	<0·001
	No	days	6 (17)	58 (49)		

duration of follow-up, as well as the thorough diagnostic procedure, without imposing on the actual treatment or rehabilitation that the patient received from the PHCC. The participation rate was high, and information on sick leave and medication could be retrieved from the electronic patient records for all included.

There were also limitations. Patients who had problems understanding the Swedish language, or other communication difficulties as well as serious health problems were probably not represented in the group of patients who accepted to participate in the study, even if we succeeded in including the number of patients estimated for reaching power in the study. This could have implications for the generalizability of the study results, at least concerning the group of patients with severe mental health diseases. However, concerning the vast group of patients with CMD treated in primary care, it is plausible to conclude that treatment with antidepressants does not influence sick leave duration.

Earlier studies in the field of CMD rehabilitation have provided little evidence for effects of single interventional measures concerning return to work. Interventions

that have included work place contact or cognitive behavioral therapy have only shown modest effects on earlier return to work, and comparisons between different antidepressants have not shown indications of different effects on return to work [13]. For complex interventions, increasing evidence shows an effect on return to work for a care manager organization at the PHCC [29]. A register study has indicated that patients receiving antidepressants have longer sick leave than those receiving other therapeutic measures [16]. In the present study, where primary care CMD patients were followed prospectively, we could, in contrast to the register study, determine whether patients treated with antidepressants constituted a different group compared to those who received psychological or other treatment. Our study could also distinguish between different diagnostic groups, severity of symptoms (mild, moderate), concurrent co-morbidity, and sick leave data by using information retrieved both from patients and electronic patient records during 12 months. Our hypothesis that antidepressant therapy causes longer sick leave than other treatment in primary care for CMD patients could not be verified.

The only other possible factor influencing sick leave duration in this observational study was shown to be the patient's own perception of return to work. This observation has earlier been described by both Swedish and Norwegian researchers [30, 31, 32] and should be regarded as an important factor to include in the rehabilitation process. The present study thus again emphasizes the importance of including the patient's own perception about return to work together with other more "objective" observations and assessments in the rehabilitation plan.

5. Conclusion

The conclusion of this prospective observational study of primary care CMD patients is that patients on sick leave with diagnoses of mild to moderate depression, anxiety syndrome, or stress-related mental illness treated with antidepressants do not return later to work than patients treated with psychological or other therapies. An important factor associated with longer sick leave time is the patient's own perception of possibility of workplace return. As CMD are important causes of sick leave and sick costs, this factor should be highlighted in future research about the rehabilitation process.

Declarations

Author contribution statement

Ingmarie Skoglund, Cecilia Björkelund, Dominique Hange: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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