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Epidemiology

Neuropsychiatric symptoms and psychotropic drug use in patients with dementia in general practices

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Abstract

Background. Neuropsychiatric symptoms (NPS) frequently occur in community-dwelling patients with dementia and they are also frequently prescribed psychotropic drugs. The prescription of psychotropic drugs has been found to be associated with the level of NPS. Data on NPS in patients with dementia in general practices are scarce.

Objectives. The aim of this study was to assess the prevalence rates of NPS and psychotropic drug use (PDU) in patients with dementia in general practices.

Methods. We analyzed data from the baseline measurement of a prospective cohort study in a sample of (Dutch) patients in general practices. Prevalence rates of NPS and subsyndromes assessed with the Neuropsychiatric Inventory (NPI) and of PDU were calculated. Prevalence rates of individual NPS are presented both as clinically relevant symptoms (NPI symptom score ≥ 4) and as prevalence rates of symptoms with symptom score > 0.

Results. Of the 117 patients, more than 90% had at least one symptom and more than 65% had at least one clinically relevant symptom. The most common NPS were agitation/aggression, dysphoria/depression and irritability/lability. The most common clinically relevant NPS were aberrant motor behaviour, agitation/aggression and apathy/indifference. Only 28.7% of the patients used at least one, 7.0% used at least two different and 1.7% used at least three different types of psychotropic drugs (excluding anti-dementia medication).

Conclusions. NPS are highly prevalent in patients with dementia in general practices, but PDU is rather low. The most common clinically relevant NPS were aberrant motor behaviour, agitation/aggression and apathy/indifference.

Key words: Dementia, mental health, pharmacology / drug reactions, primary care.

Introduction

Dementia is a syndrome that affects memory, thinking, behaviour and the ability to perform everyday activities ([1]). Most people with dementia reside in the community. In the Netherlands, it is estimated that there are 260.000 people with dementia of whom approximately 70% are community-dwelling i.e., not live in a long-term care

facility (LTCF). Of these, 60% live with their informal caregiver and 40% alone (2,3). Over the course of the disease most of them will experience some type of neuropsychiatric symptoms (NPS) (4). NPS include psychiatric and behavioural symptoms, such as delusions, hallucinations, depressive symptoms, anxiety, euphoria, agitation, aggression, apathy, and disinhibition.

Recent studies in various countries reported NPS prevalence rates for community-dwelling people with dementia that ranged from 44% to 96% measured with the Neuropsychiatric Inventory (NPI) (5–21). Apathy, agitation/aggression, dysphoria/depression, irritability/lability, anxiety and aberrant motor behaviour were the most common NPS (5–11,13–16). Prevalence rates of clinically relevant symptoms (NPI symptom score ≥ 4) are lower: 44% to 81%, compared to NPI symptom score > 0: 88% to 96% (5–11).

Half of the former studies conducted on NPS in community-dwelling people with dementia were community-based studies, but the number of people who were living at home versus those living in a LTCF were either not given or up to one-third appeared to be living in a LTCF. The other half of the studies were conducted on ambulatory patients with dementia visiting outpatient memory, (old age) psychiatry, neurological and geriatric clinical centers or dementia services, which is considered secondary care. Three to 36% of these study populations also lived in a LTCF. In the Netherlands, general practitioners (GPs) provide basic medical care for people who live at home. For LTCF there are specifically trained medical doctors called elderly care physicians (22,23). Only a small proportion of people in general practice in the Netherlands are referred to secondary care. Therefore, it is likely that a study population visiting outpatient clinical centres have more severe and frequent symptoms than the total group of people with dementia in general practices. For GPs, it is important that accurate data of NPS of patients with dementia in general practices are available. To date only one German study reported prevalence rates of NPS in general practices (11,13).

Psychotropic drugs, such as antipsychotics, are frequently prescribed in patients with dementia with agitation, psychosis and anxiety. The prevalence of psychotropic drug use (PDU) is related to the prevalence of NPS (11,24). Almost 66% of the people with dementia in primary care in Germany use at least one psychotropic drug and the use of antipsychotics is associated with higher NPI scores (11). In Finland, 53% of the people with dementia use at least one and 20% use at least two psychotropic drugs with a prevalence rate of antipsychotic use of 20–22% (24,25). There is only limited evidence for the effectiveness of psychotropic drugs in the treatment of NPS in people with dementia and psychotropic drugs cause serious adverse effects, like extrapyramidal symptoms, accelerated cognitive decline, stroke and death. Only some atypical antipsychotic drugs have shown benefit in the treatment of aggression in people with Alzheimer's disease over a period of up to 12 weeks (26). Selective serotonin re-uptake inhibitors or serotonin-specific re-uptake inhibitors (SSRIs) have been proposed as an alternative pharmacological approach to antipsychotics based on evidence that the serotonergic system is involved in the etiology of NPS in dementia (27). For example citalopram compared with placebo significantly reduces agitation and caregiver distress. However, cognitive and cardiac adverse effects of citalopram may also limit its practical application (28).

NPS, especially depression, are predictors of institutionalization (29,30). They are also associated with psychological distress in informal caregivers (31–34).

To date, only one study reported prevalence rates of NPS and PDU in general practices. The DelPhi-MV study, a cohort study in general practices in Germany, found that 43.8% of the patients had one or more clinically relevant NPS in the previous 4 weeks and almost 66% of the study population used at least one psychotropic drug including anti-dementia medication (11,13). Thus, data are scarce while they are very relevant for general practices, because the general practitioner (GP) is most often the first physician consulted for dementia-related problems and NPS frequently lead to institutionalization, high rates of PDU and psychological distress in their informal caregivers.

Therefore, the aim of this study was to assess the prevalence of NPS and the prevalence of PDU in patients with dementia in general practices.

Methods

This is a cross-sectional analysis of baseline measurements from a prospective naturalistic cohort study with a follow-up of 18 months. All participants were living at home and cared for by an informal caregiver. This study has been described in detail previously (35). We invited all 192 known GPs in 114 general practices in the region West- and Middle-Brabant. These practices are representative for the Dutch general practices because the practice/GP ratio in West- and Middle-Brabant (59%) is comparable to the ratio of the Netherlands (58%) (36). Eventually, 37 GPs in 18 general practices participated in this study. These 18 general practices in the study are representative for the Dutch general practices because the percentages of single-handed/two-person/group practices seem to be rather comparable (22% to 28% single handed, 33% to 39% two-person practice, 44% to 33% group practice) and because the mean number of patients per practice is comparable (2062 versus 2200).

Patients and informal caregivers

We successively screened the 18 participating practices between January and July 2012 to identify and recruit dyads of patients and informal caregivers. Eligible patients were selected with a search in the electronic medical files. It took 7 months to visit all practices, selection was done at one specific moment in time. These patients and their caregivers were approached by mail. The GP contacted patient or informal caregiver by telephone to stimulate participation in the study. Inclusion criteria for patients were: living at home and registered in the GP's electronic medical file with a diagnosis of dementia. Dutch GPs code all diagnoses in their files according to the International Classification of Primary Care (ICPC) (37). According to the ICPC dementia is coded as P70 and memory disturbance as P20. Patients living in a LTCF or with an estimated life expectancy of less than three months were excluded. This research project was presented for medical ethics review at the regional Committee on Research Involving Human Subjects (CMO). The committee judged that this project, according to the Dutch legislation, could be carried out without formal approval by the CMO. Patients, or their legal representatives, and caregivers gave written informed consent.

Assessment instruments

Clinical characteristics of patients and informal caregivers were collected by a trained research assistant during an interview with the patient and the informal caregiver at their home. NPS of the patients were assessed with the Neuropsychiatric Inventory (NPI) ranging from 0 to 144 (17,21,38). Based on previous studies we categorized the NPI in three behavioural subsyndromes: mood/apathy (depression, apathy, night-time behaviour disturbances, and appetite and eating abnormalities), psychosis (delusions and hallucinations),

and hyperactivity (agitation, euphoria, irritability, disinhibition, and aberrant motor behaviour). Anxiety was regarded as a separate symptom (39). Cognition of the patient was assessed with the Mini-Mental State Examination (MMSE) ranging from 0 to 30 (40).

Data about PDU were obtained on the day of assessment during the interview with the patient and the informal caregiver. All drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system: antipsychotics (N05A), antiepileptic medication (N03A), antidepressants (N06A), anxiolytics (N05B), hypnotics (N05C) and anti-dementia medication (N06D) (41). For antipsychotics we made a distinction between typical/classical, (first-generation antipsychotics), and atypical, (second-generation antipsychotics). For antidepressants we made a distinction between selective serotonin re-uptake inhibitors (SSRI's) and tricyclic antidepressants. Anti-dementia medication included the use of an acetylcholinesterase inhibitor (AChEI: rivastigmine and galantamine) or a N-methyl-d-aspartate receptor antagonist (NMDAR: memantine) (42).

Prevalence of NPS

The prevalence of NPS was calculated by dividing the number of participants who exhibit NPS in the previous 4 weeks by the number of participants in our study population. Each symptom score of the NPI was defined by a frequency (F) times severity (S) score. Generally a symptom score of 4 or higher is considered clinically relevant (6–8). Prevalence rates of individual NPS are presented both as clinically relevant symptoms (NPI symptom score ≥ 4) and as prevalence irrespective of clinical relevance (NPI symptom score > 0).

Psychotropic drug use

The prevalence of psychotropic drugs and combinations of these were calculated by dividing the number of participants who use one or more psychotropic drugs by the number of participants in our study population.

Data analysis

We summarized the demographic and clinical characteristics of the participants by descriptives. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) 23.0. For missing items for the NPI we used ipsative mean imputation, which substitutes the missing items by the mean of the remaining items within the individual (43,44). We accepted 1 missing item in the NPI for the NPI total score and no missing items for the NPI subsyndromes.

Results

The participating general practices in our study are representative for the Netherlands for the types of general practices. We do not have data about characteristics such as age, gender and socioeconomic status of the total patient population of the participating practices. We have incomplete data of the age distribution in the 18 participating practices. In 10 of these practices, the percentage of patients aged 75 and older is 22.5%. In total 243 patients with dementia were identified of whom 117 (48%) were included (Figure 1). The mean age of the 126 patients who refused (*n* = 121) or withdrew (*n* = 5) their consent was 79.2 years (SD 6.8) and 67% were female. The mean age of the informal caregivers who refused or withdrew their consent (missing data *n* = 31) was 66.0 years (SD 14.0, range 28–92) and 67% were female (missing data *n* = 2). The relation of the informal caregiver with the patient (missing data *n* = 4) was 49% spouse, 45% child and 6% others. The 126 patients who refused or withdrew their consent were more often female; informal caregivers of these patients were more often child. Two patients were admitted to a LTCF after informed consent and just before baseline assessment. They entered the study and the baseline questionnaires were filled out as before institutionalization.

Clinical characteristics of the patients and informal caregivers

Patients of the study population had a mean age of 78.6 years (SD 7.1) and 52% were female (Table 1). Only 4% of these patients had an age less than 65 years. Mean NPI total score was low (15.7, range 0–77). Use of health care services were: case manager (29.3%), day care centres (34.2%), home care services (47.9%) and domestic care (47.9%).

Informal caregivers of the patients had a mean age of 67.3 years (SD 13.3, range 32–92) and 68.4% were female, 65.0% were spouse, 29.1% child or child-in-law and 5.9% were others, like grandchild, sibling, friend/acquaintance, neighbour or nephew or niece.
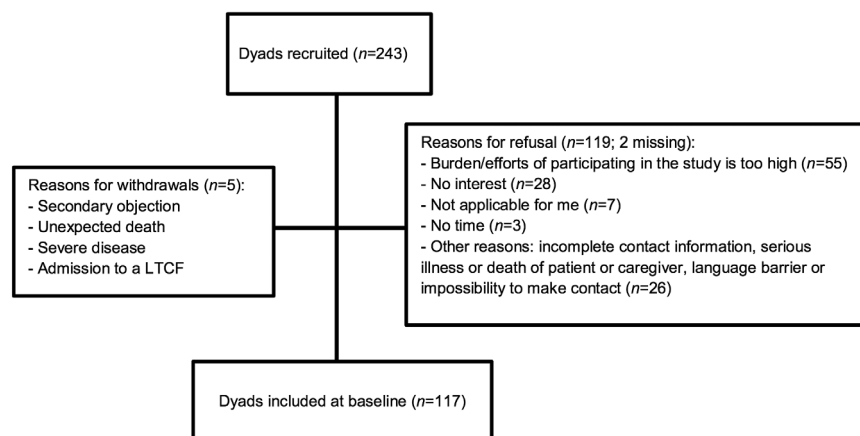

Figure 1. Recruitment of patients with dementia in general practice (2012). Dyads = patient and caregiver; LTCF: Long term care facility; *n* = number of participants

Table 1. Characteristics of patients with dementia and informal caregivers (*n* = 117) in general practice (2012)

Patients	Participants (*n* = 117)	Refusals/withdrawals (*n* = 126)
Age (years)		
Mean ± SD	78.6 ± 7.1	79.2 ± 6.8
Range	57–91	63–92
Gender (*n* (%))		(*n* = 89)
Male	56 (47.9)	42 (33.3)
Female	61 (52.1)	84 (66.7)
Race (*n* (%))		
Caucasian	115 (98.3)	
Other	2 (1.7)	
Level of profession (*n* (%))		
Elementary occupation	23 (19.7)	
Lower occupation	22 (18.8)	
Secondary profession	48 (41.0)	
Higher profession	18 (15.4)	
Scientific profession	6 (5.1)	
Marital status (*n* (%))		
Married	80 (68.4)	
Widow	33 (28.2)	
Divorced	1 (0.9)	
Unmarried	3 (2.6)	
Use of care services (*n* (%))		
Case manager	34 (29.3)	
Day care centers	40 (34.2)	
Home care services	56 (47.9)	
Domestic care	56 (47.9)	
Psychotropic medication (*n* (%))	(*n* = 114)	
No psychotropic medication	54 (47.0)	
Antipsychotics	11 (9.6)	
Typical or classic	5 (4.3)	
Atypical	7 (6.1)	
Antiepileptics	6 (5.2)	
Antidepressants	20 (17.4)	
Non-tricyclic/SSRIs	19 (16.5)	
Tricyclic	1 (0.9)	
Anxiolytics	3 (2.6)	
Hypnotics	2 (2.6)	
Anti-dementia	39 (33.6)	
AChEI	39 (33.6)	
NMDAR	2 (1.7)	
MMSE-score	(*n* = 97)	
Mean ± SD	19.5 ± 5.6	
Range (0–30)	0–27	
Score 20+ (Mild) (*n* (%))	63 (57.8)	
Score 10–19 (Moderate) (*n* (%))	31 (28.4)	
Score 0–9 (Severe) (*n* (%))	15 (13.8)	
NPI total score	(*n* = 116)	
Mean ± SD	15.7 ± 15.4	
Range (0–144)	0–77	
Informal caregivers		
Age (years)		(*n* = 95)
Mean ± SD	67.3 ± 13.3	66.0 ± 14.0
Range	32–92	28–93
Gender (*n* (%))		(*n* = 124)
Male	37 (31.6)	41 (33.1)
Female	80 (68.4)	84 (66.9)
Relationship to the patient (*n* (%))		(*n* = 122)
Spouse	76 (65.0)	60 (49.2)
Child/child-in-law	34 (29.1)	55 (45.1)
Other	7 (5.9)	7 (5.7)

n: number of participants; SSRIs: Selective serotonin re-uptake inhibitors; AChEI: acetylcholinesterase inhibitor; NMDAR: N-methyl-d-aspartate receptor antagonist; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatric Inventory.

Prevalence of NPS

Almost all patients (92.2%) had one or more NPS, whereas 65.5% had one or more clinically relevant NPS. Prevalence rates of NPS are presented in Figure 2. The most common NPS (NPI symptom score > 0) were agitation/aggression (54.3%), dysphoria/depression (52.6%) and irritability/lability (48.3%). The most common clinically relevant NPS (NPI symptom score ≥ 4) were aberrant motor behaviour (28.4%), agitation/aggression (23.3%) and apathy/indifference (21.6%). Prevalence rates of NPI subsyndromes for NPI symptom score > 0 and clinically relevant NPS were: mood/apathy 81.0% and 47.0%, psychosis 23.3% and 9.6%, hyperactivity 80.2% and 48.7%, respectively.

Psychotropic drug use

Prevalence rates of PDU are presented in Table 1. Almost half (47.0%, *n* = 54) of the patients in our study population did not use psychotropic drugs at all, 53.0% (*n* = 61) used at least one, 13.9% (*n* = 16) used at least two and four patients (3.5%) used three different psychotropic drugs. When leaving out anti-dementia medication 71.3% (*n* = 82) used no psychotropic drugs at all, 28.7% (*n* = 33) used at least one, 7.0% (*n* = 8) used at least two different psychotropic medications and two patients (1.7%) used three different psychotropic drugs. Of the six patients who used antiepileptics, one was for focal epilepsy, two for leg pain.

Discussion

We found that NPS are very common in people with dementia in general practices. More than 90% of the study population had at least one NPS and more than 65% had at least one clinically relevant NPS. The most common NPS were agitation/aggression, dysphoria/depression and irritability/lability. The most common clinically relevant NPS were aberrant motor behaviour, agitation/aggression and apathy/indifference. Almost 29% of the patients used at least one, 7.0% used at least two different and 1.7% used at least three psychotropic drugs (excluding anti-dementia medication).

Compared to the DelpHi-MV study, the prevalence of all symptoms of the NPI in our study are higher. The most common NPS in this study were dysphoria/depression 36.8%, apathy 32.2%, agitation/aggression 31.0%, which is, except for apathy, in line with the findings of our study (13). In the DelpHi-MV study, GP practices screened patients aged 70 years and older for dementia and only 81 of the 176 (46%) people with dementia in this cohort were already diagnosed before start of the study. Because of this under-reporting of GPs the study population in our study is probably in a more advanced stage of the disease. The mean MMSE score in our study (19.5 ± 5.6) is lower than in the DelpHi-MV study (20.87 ± 5.6).

Except for delusions and hallucinations, all other symptoms and subsyndromes on the NPI in our study were more prevalent than in the DelpHi-MV study. The most common clinically relevant symptoms in the DelpHi-MV study were apathy 15.3%, aberrant motor behaviour 11.4%, anxiety 10.2%, which is, except for anxiety in line with our findings (11). On the other hand, compared to the MAAstricht Study of BEhaviour in Dementia (MAASBED) study, a prospective Dutch study on a cohort of psychiatric-based clinics, the prevalence rates we found were lower for the majority of the clinically relevant symptoms and subsyndromes on the NPI (10 out of 15) except for agitation/aggression, disinhibition, aberrant motor behaviour, night-time behaviour disturbance and the hyperactivity subsyndrome. Especially for delusions and hallucinations (psychosis subsyndrome), dysphoria/depression, apathy/indifference and the mood/apathy subsyndrome our prevalence rates were much lower. Mean MMSE score in the MAASBED study was lower: 18.09 (4.68), as compared to our study as we expected in an ambulatory psychiatry-based study (10).

PDU in our study (28.7% at least one excluding anti-dementia medication) is higher compared to the findings of the Dutch study
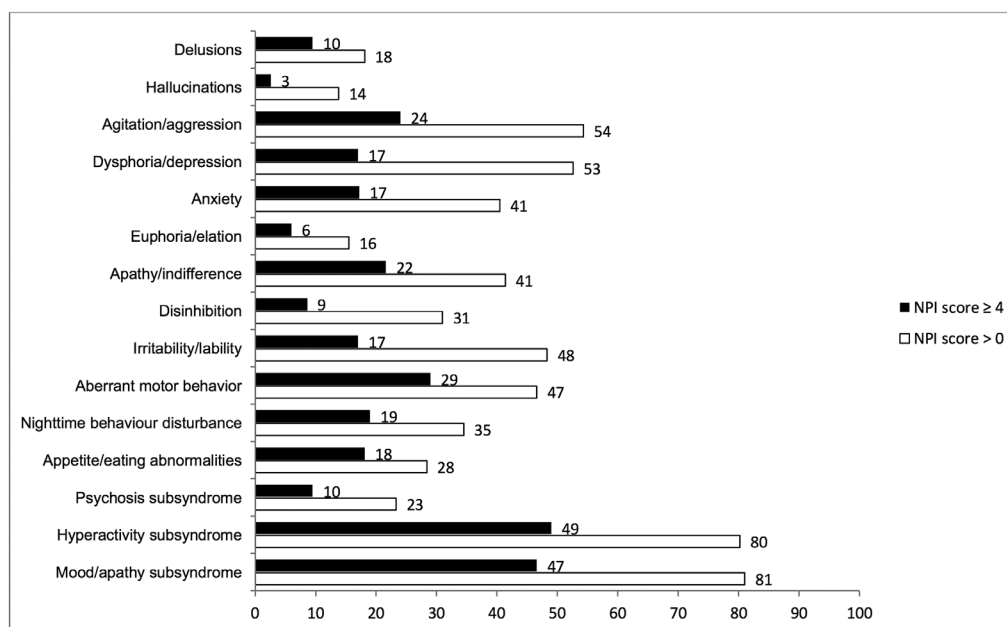

Figure 2. Prevalence of neuropsychiatric symptoms in patients with dementia (*n* = 116) in general practice (2012). Neuropsychiatric Inventory (NPI) score > 0: percentage of patients who exhibit the symptom on the NPI (*n* = 116; 1 missing); NPI score ≥ 4: percentage of patients with clinically relevant score on the NPI (*n* = 115; 2 missing); Psychosis subsyndrome: delusions and hallucinations; Hyperactivity subsyndrome: agitation, euphoria, disinhibition, irritability, and aberrant motor behaviour; Mood/apathy subsyndrome: depression, apathy, night-time behaviour disturbances, and appetite and eating abnormalities

of Hamers et al. (16.0%) in 2016. However, this study was conducted on people with cognitive impairment, not specifically with a diagnosis of dementia. And secondly, they were all supported by a case manager, compared to 29.3% in our study. PDU including antidementia medication (53.0% at least one) in our study is lower compared to the DelpHi-study (66%). Use of antipsychotics in our study (9.6%) is relatively low compared to the studies in Germany (10.6 to 13.6%), Finland (20 to 22.1%) and the United States of America (USA) (27%) (11,13,24,25,45). Only in Sweden the antipsychotic use is lower (4.2%) (46). The use of antiepileptics (5.2%) in our study is lower than in Germany; use of antidepressants (17.4%) is higher than in Germany (14.0 to 15.3%), but lower than in Sweden (22.9%) and Finland (28%) (11,13,25,45,46). The use of anxiolytics (2.6%) and hypnotics (2.6%) in our study is much lower than in Sweden (6.9% and 13.3%, respectively) (46). Use of anti-dementia medication (33.6%) is similar to the studies in Germany (25.8 to 42%) and low compared to Sweden (75.4%), where the use of AChEI is recommended in the national guidelines for all people with Alzheimer's disease (11,13,46). In this Swedish study it was found that patients taking an AChEI were treated with less antipsychotics and anxiolytics than those not taking an AChEI. Overall, in our study PDU is relatively low compared to other studies, specifically if you take into account the high prevalence rates of NPS we found. Dutch GPs and their guidelines are generally very reticent in prescribing psychotropic drugs (36).

Strengths and limitations

The sample of patients and informal caregivers in this study was heterogeneous with patients in all stages of dementia and they were included from general practices. The participating general practices in our study are representative for the Dutch general practices. Data included PDU.

A limitation to our study is the rather low participation of general practices (114 invited, 18 participated) and high refusal rate of patients and informal caregivers indicating that burden of participating in the study is too high. Due to this there is a risk that we have studied a selective group of patients with relatively low levels of NPS. On the other hand, GPs often wait before diagnosing dementia which may have biased our sample towards a more severe spectrum of people with dementia and NPS. The difference in clinical characteristics between the participants and those who refused or were withdrawn, also gives a risk of selection bias. The percentage of patients aged over 75 in the participating general practices (22.5%) is probably higher than in the Dutch general population (9.6%) (36). This overestimates the number of patients with dementia, NPS and PDU compared to the average general practice in the Netherlands.

Finally, caregivers who experience high levels of psychological distress may score the NPS of the person with dementia they care for as more severe. Higher frequency of NPS is associated with higher levels of psychological distress (34). This results in caregiver-rating bias, which could have affected the level of NPS to a more severe spectrum (16,47).

Implications

We expected less severe and frequent NPS in patients with dementia in general practices compared to ambulatory patients visiting outpatient clinical centers, but this study showed that a high proportion of patients with dementia in general practices have at least one (clinically relevant) NPS. The prevalence of PDU in our study is low compared to other studies but still almost 29% of the patients with dementia has a prescription for at least one psychotropic drug. The GP is often the first person to be consulted for patients who are worried that they may have dementia or for dementia-related problems like NPS. A timely diagnosis of dementia is important to be able to provide adequate post-diagnostic support, such as psycho-education, access to treatment and psychosocial interventions, peer support, advance care planning and advance directives (48). Many psychosocial interventions for people with dementia and their informal caregivers have been developed in the last decades and they have proven to be more effective and give less adverse effects than prescribing psychotropic drugs (49–51). Cognitive stimulation or multicomponent interventions, in which cognitive stimulation is combined with reminiscence and relaxation or support, or behavioural interventions performed by individual work with the informal caregiver have been shown to be effective on NPS (49). Multicomponent interventions as cognitive stimulation combined with reminiscence or physical exercise or ADL training or support have been shown to be effective in improving the mood of the people with dementia (49). NPS in people with dementia require a timely diagnosis and adequate professional support to diminish NPS and prevent institutionalization and psychological distress in their informal caregivers.

Declaration

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