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Original article

Treatment patterns and costs in patients with generalised anxiety disorder: One-year retrospective analysis of data from national registers in Sweden

R. Sandelin [a,*], J. Kowalski [b], E. Ahnemark [a], C. Allgulander [b]

[a] Pfizer AB, Vetenskapsvägen 10, 191 90 Sollentuna, Sweden
[b] Karolinska Institutet, 141 86 Stockholm, Sweden

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ABSTRACT

Purpose. – To investigate medication use, direct healthcare costs and comorbidities in patients with generalised anxiety disorder (GAD) within specialised care in Sweden 2006–2007.
Methods. – A retrospective study was conducted using data from the National Patient Register and the Swedish Prescribed Drug Register. All patients with a primary GAD (ICD-10) diagnosis in 2006 were followed for 12 months to study medication use and health care consumption. Resource use was evaluated from the number of hospitalisation episodes, number of visits to outpatient care and medication dispensed. Costs were calculated by multiplying the number of visits and hospitalisation episodes with the corresponding unit costs. Descriptive statistics were used for all analyses.
Results. – Three thousand seven hundred and one patients with a primary GAD diagnosis were included in the study. Thirty-four percent of the patients ($n = 1246$) had at least one secondary comorbid diagnosis. SSRIs/SNRIs were the most commonly dispensed medications, followed by benzodiazepine-anxiolytics, hypnotics and antihistamines. The mean number of treatment days for all medications prescribed and dispensed was highest (1144 days) for elderly women aged 65 years or more (treatment days per patient could exceed 365 days due to multiple concomitant medication use). Elderly patients were frequently prescribed benzodiazepine-anxiolytics ($n = 92/117$ men [79%]; $n = 238/284$ women [84%]) and hypnotics ($n = 70$ men [60%]; $n = 178$ women [63%]) compared to the overall study population ($n = 612/1303$ men [47%] and $n = 935/2398$ women [39%], respectively). GAD-related direct costs accounted for 96% of all direct costs. Mean number of hospitalisation days and corresponding costs were high (19 days; SEK 92,156; $n = 358$ [9.7%]) in relation to medication (SEK 5520; $n = 3352$ [91%]) and outpatient costs (SEK 7698; $n = 3461$ [94%]).
Conclusions. – The high rate of polypharmacy, significant psychiatric comorbidity and widespread use of benzodiazepine-anxiolytics and medications not indicated for GAD suggest that the disease burden is high. Total direct costs associated with the disease were high but still likely to be underestimated.

1. Introduction

Generalised anxiety disorder (GAD) is a chronic anxiety disorder defined as excessive and uncontrollable worry about everyday life situations. GAD is one of the most common anxiety disorders seen by primary care physicians, although it is frequently under-recognised and often misdiagnosed [36,46]. European epidemiological data suggest that around 2% of all adults are affected over a 12-month period and that women are two to three times more likely to suffer from GAD as men [25]. Lifetime estimates of the prevalence of GAD vary, but are generally within the range of 2–6% among the adult general population worldwide [24,25,47]. Prevalence rates are particularly high in midlife and in the elderly [46]. In one study, GAD was the most frequently reported anxiety disorder among Dutch patients aged 55 to 85 years [7], and around half of elderly individuals with GAD in a US sample reported late-onset GAD [13]. In Scandinavia, GAD and/or depression prevalence is high and up to one-half of the cases were identified by general practitioners in one study [29].

The human and economic burden of GAD is high. GAD adversely affects work performance and psychosocial functioning, increases disability and has a significant impact on health-related quality of life, particularly later in life [33,34]. Patients with GAD also experience a high degree of comorbidity. Around 90% present with at least one additional lifetime psychiatric disorder [47], and lifetime comorbidity with depression is approximately 60% [22]. Somatic conditions such as chronic pain, gastrointestinal disorders, diabetes and cardiac symptoms are also frequently reported

* Corresponding author. Tel.: +46 768892278, fax: +46 855052010.
E-mail address: rebecka.sandelin@pfizer.com (R. Sandelin).

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[10,14,18]. Consequently, GAD is associated with considerable economic costs as a result of lost work productivity and high levels of medical resource utilisation [19].

Treatment strategies for GAD have changed considerably over the past 10 years. Current evidence-based guidelines recommend initial treatment with an antidepressant, either a selective serotonin reuptake inhibitor (SSRI) such as sertraline, paroxetine or escitalopram, or a serotonin noradrenaline reuptake inhibitor (SNRI), either duloxetine or venlafaxine [5,6]. The calcium channel modulator pregabalin was also approved for GAD in 2006 and is recommended as a first-line treatment by the World Federation of Societies of Biological Psychiatry (WFSBP) [6]. Benzodiazepine-anxiolytics are indicated as a short-term strategy to obtain immediate symptomatic relief, but their use is not generally recommended for more than a few weeks. Treatment guidelines are useful tools for assisting physicians in clinical decision-making. However, recommendations are largely based on the results of controlled trials in highly selected symptomatic patients and do not necessarily mirror real-life situations for the prescription of medication in GAD patients with multiple comorbid conditions [1]. A recent evidence-based review on the pharmacotherapy of GAD was published in January 2011 [5]. The authors concluded that there have been few investigations of the management of patients who have not responded to first-line treatment, despite the fact that switching to another evidence-based treatment or use of augmentation strategies may be beneficial.

Several studies have investigated healthcare costs associated with GAD [9,19], but few studies have been conducted anywhere on treatment patterns and resource utilisation in patients in specialised care. Moreover, the economic burden of GAD in Sweden is currently unknown. Therefore, the aim of this study was to investigate medication use, direct healthcare costs and comorbidities in patients with a primary ICD-10 GAD diagnosis within specialised outpatient and inpatient care in Sweden between 2006 to 2007.

2. Methods

2.1. Study population

This was a retrospective study that combined data from the National Patient Register and Swedish Prescribed Drug Register [44]. The study was approved by the Regional Research Ethics Review Board (Stockholm, Sweden). Source data are the property of the National Board of Health and Welfare, Sweden. Data were made anonymous prior to analysis. All patients who were recorded with an ICD-10 diagnosis of GAD F41.1 in specialised care in Sweden during 2006 were eligible. Patients were identified from the National Patient Register, which covers all inpatient care episodes and most specialised outpatient care visits, and records both primary and secondary diagnosis codes. A primary diagnosis is defined as the main diagnosis for which the patient is treated at a given visit; a secondary diagnosis is any other diagnosis registered by the physician that is not the main reason for treatment. A total of 5284 patients with primary/secondary GAD were recorded. However, in order to reduce sample heterogeneity, only data for patients with a primary GAD diagnosis were included in the final analysis population.

2.2. Data and statistical methods

Patients were monitored in the registers for 12 months after the first inpatient or outpatient visit with GAD as a primary diagnosis during 2006, which were the study inclusion criteria. The primary study outcomes were medication treatment patterns and resource use. Data on medication use were obtained from the Swedish Prescribed Drug Register, which stores records of the date and amount of prescription drugs dispensed by pharmacies to individuals. These data were linked to data from the National Patient Register via personal identification numbers. Medications were grouped into pharmacological categories (Table 1) and treatment patterns studied using descriptive statistics. Only psychoactive medications were included in the analyses, i.e. substances that act primarily on the central nervous system to alter brain function, resulting in changes in perception, mood, consciousness, or behaviour [38]. Dispensed prescriptions were recorded with the dose schedule, number of packages and number of tablets per package; from this, the number of treatment days for each patient was calculated by medication and pharmacological category. The sum of treatment days per patient could exceed 365 days when medications were used in parallel, or if prescriptions were allocated for a longer duration than our study period of 12 months.

Resource use was evaluated from the number of hospitalisation episodes and number of visits to outpatient care. Records for hospital admissions and outpatient visits were obtained from the National Patient Register. An inpatient care record covered one inpatient episode and its duration (in days), starting from the point of inpatient admission and ending with inpatient discharge. An outpatient visit was defined as an occasion where a patient was seen by a specialist in public outpatient care. Outpatient visits and inpatient episodes were categorised as either GAD- or non-GAD-related; visits/episodes recorded with a primary diagnosis other than GAD were classified as non-GAD-related. Outpatient and inpatient costs were calculated for the 12-month period following the date in 2006 of the first recorded primary GAD diagnosis. Outpatient costs were calculated by multiplying the number of visits with the corresponding unit cost. Inpatient costs were calculated by multiplying the number of inpatient days with the corresponding cost per bed-day [39,41]. The length and number of

Table 1
Medication categories.

Drug category	
SSRIs	Escitalopram, paroxetine, sertraline, citalopram, fluoxetine, fluvoxamine
SNRIs[a]	Venlafaxine, duloxetine, mirtazapine, mianserin
Antiepileptics	Pregabalin, gabapentin, lamotrigine
TCAs	Clomipramine, nortriptyline, amitriptyline, trimipramine
Phenothiazines	Chlorpromazine, haloperidol, flufenazine, levomepromazine, perfenazine, prochlorperazine, flupentixol, chlorprotixene, zuclopentixol
Antipsychotics	Quetiapine, olanzapine, risperidone, ziprasidone, aripiprazole, sertindole, clozapine
BZD-anxiolytics	Diazepam, oxazepam, alprazolam, lorazepam
Hypnotics	Flunitrazepam, nitrazepam, triazolam, zaleplon, zopiclone, zolpidem
Antihistamines	Propiomazine, alimemazine, promethazine, hydroxizine
Other	Buspirone

SSRIs: selective serotonin reuptake inhibitors; SNRIs: selective noradrenaline reuptake inhibitors; TCAs: tricyclic antidepressants; BZD: benzodiazepine.
[a] Includes mirtazapine and mianserin (act by modulating synaptic turnover of noradrenaline and serotonin).

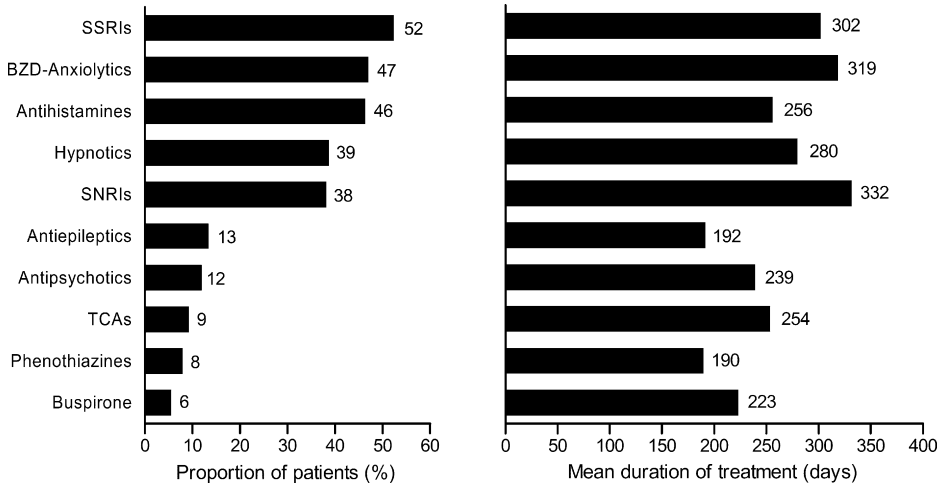


Fig. 1. Medication treatment patterns in patients diagnosed with primary GAD (n = 3701). Medications were delivered to the patient by pharmacies. SSRIs: selective serotonin reuptake inhibitors; BZD: benzodiazepine; SNRIs: serotonin noradrenaline reuptake inhibitors; TCAs: tricyclic antidepressants.

hospital admissions were multiplied with appropriate unit costs. Medication costs were obtained from the Swedish Prescribed Drug register, which stores records of all costs at pharmacy selling price. Medication costs during inpatient care periods were included in the cost per bed-day and thus not counted separately. Total direct costs for GAD were calculated as the sum of costs for inpatient care, outpatient care and medication supply. The currency used was the Swedish Krona SEK and conversion to EUR was based on the exchange rate in December 2011 (1 EUR = SEK 9.02).

Multivariate logistic regression analysis was used to explore the relationship between discriminant factors (age, gender and presence of additional ICD-10 diagnoses) and the use of specific GAD treatments. Results are presented as the odds for monotherapy with a SSRI or SNRI, an anxiolytic or an antipsychotic respectively. All tests were two-sided and $P < 0.05$ was regarded as statistically significant. Calculations and analyses were performed using STATISTICA, versions 8 and 9, StatSoft Inc., Tulsa, US.

3. Results

3.1. Population characteristics

In total, 3701 patients (n = 2398 women [65%]) treated in specialised care were identified with an ICD-10 diagnosis of primary GAD. The mean (SD) age was 44 (16.4) years and the proportion of patients more or equal to 65 years of age was 11% (n = 401). Three thousand four hundred and sixty-one patients (94%) with primary GAD received specialised outpatient care, 358 (10%) received inpatient care, and 147 (4%) received both outpatient and inpatient care.

3.2. Dispensed medications

A total of 81,704 prescriptions for psychoactive medications were dispensed for 3352 patients (91%) with a primary GAD diagnosis during the 12-month follow-up period. Fig. 1 shows the distribution of dispensed prescriptions according to pharmacological category, along with the mean treatment duration for each type of medication. SSRIs represented the largest drug category (dispensed to 1938 patients [52%]), followed by benzodiazepine-anxiolytics (n = 1740 [47%]), antihistamines (n = 1714 [46%]), hypnotics (n = 1434 [39%]) and SNRIs (n = 1413 [38%]). The number of treatment days covered by the delivered prescriptions was highest for patients on SNRIs (mean duration, 332 days), followed by benzodiazepine-anxiolytics (319 days) and SSRIs (302 days). Atypical antipsychotics were dispensed to 442 patients (12%) with a mean duration of treatment of 239 days.

Polypharmacy was common. The total mean number of days of medication dispensed per patient across all 10 pharmacological categories during the 12-month follow-up period was 847 days, and 71% (n = 2646) of the study population received medications from two or more pharmacological categories. The most frequently prescribed drug class combinations with SSRIs or SNRIs are shown in Fig. 2. Overall, 73% (n = 2713) of all patients were prescribed treatment with SSRIs or SNRIs: 511 patients (14%) were dispensed prescriptions for only SSRIs or SNRIs, and 2202 (59%) received SSRIs/SNRIs in combination with other psychoactive drugs. In total, 37% of the study population (n = 1370) were prescribed treatment combinations that included SSRIs/SNRIs and benzodiazepine-anxiolytics, and 31% (n = 1164) received combinations that included SSRIs/SNRIs and hypnotics.

Fig. 3 shows medication treatment patterns according to gender and age ($<$ 65 years and $\geq$ 65 years). Benzodiazepine-anxiolytics were more frequently dispensed to elderly patients (n = 92 men [79%]; n = 238 women [84%]) than to younger patients (n = 529 men [49%]; n = 881 women [47%]). Similarly, the proportion of patients who took hypnotics was notably higher in older (n = 70 men [60%]; n = 178 women [63%]) versus younger patients (n = 427 men [40%]; n = 759 women [41%]). Elderly men

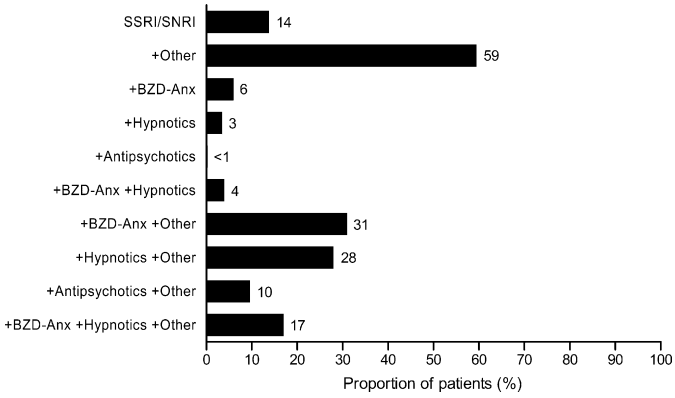


Fig. 2. Drug treatment of primary GAD: distribution of pharmacological categories prescribed in combination with SSRIs or SNRIs. SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin noradrenaline reuptake inhibitor; BZD-anx: benzodiazepine-anxiolytic.

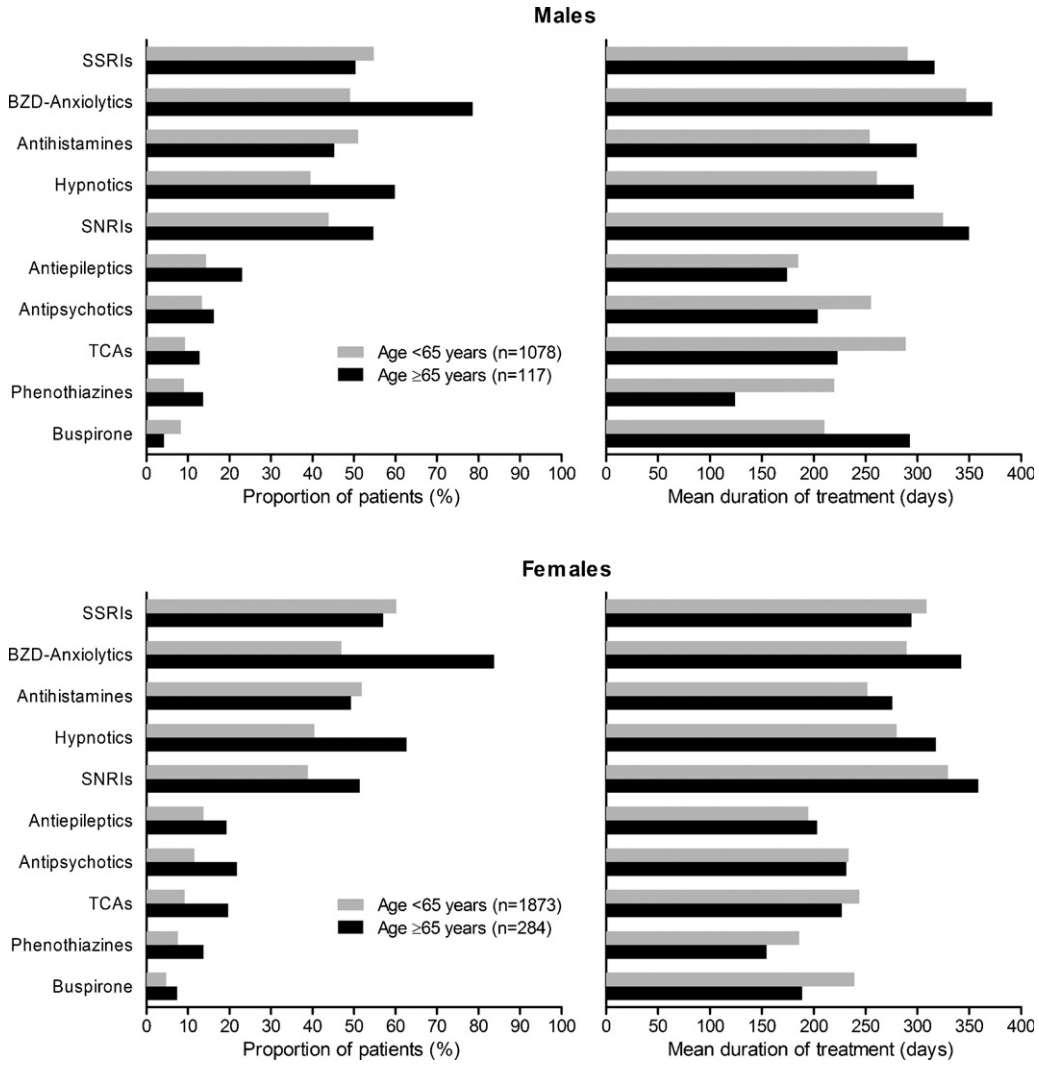


Fig. 3. Medication treatment patterns in patients diagnosed with primary GAD by gender and age group. SSRIs: selective serotonin reuptake inhibitors; BZD: benzodiazepine; SNRIs: serotonin noradrenalin reuptake inhibitors; TCAs: tricyclic antidepressants; *n*: number of subjects.

received benzodiazepine-anxiolytics for the longest mean duration (372 days), whereas the mean duration of hypnotic use was highest in elderly women (318 days). Elderly women were the most frequent consumers of antipsychotic agents (22% [$n = 62$]).

For both sexes, the total mean number of treatment days across all pharmacological categories was higher in older (≥ 65 years) than younger (< 65 years) patients. The mean treatment duration was 1088 days ($n = 117$) in elderly men and 1144 days in elderly women ($n = 284$), compared with 830 days in younger men ($n = 1078$) and 796 days in younger women ($n = 1873$) (Table 2). Among elderly patients, 88% ($n = 103$) of men and 93% ($n = 263$) of women received medications from two or more pharmacological categories (compared to 78% [$n = 846$] of men and 77% [$n = 1434$] of women in the younger age group), and 70% ($n = 82$) of men and 78% ($n = 221$) of women received drugs from three or more categories (53% [$n = 573$] of men and 52% [$n = 968$] of women in the younger age group) (Table 3).

3.3. Comorbid diagnoses

During the 12-month study period, 34% of patients ($n = 1246$) with primary GAD had at least one secondary diagnosis (any comorbidity), and 26% of these ($n = 324$) were diagnosed with two or more conditions. Secondary psychiatric and somatic diagnoses are shown in Fig. 4. The most frequently reported comorbid psychiatric conditions were depressive syndromes ($n = 406$ patients), other anxiety disorders ($n = 284$ patients), personality disorders ($n = 204$), and substance-induced disorders ($n = 183$). The category of neurodevelopmental disorders was relatively frequently reported ($n = 111$) and included different degrees of mental retardation (ICD-10 F70-F89). Alzheimer's disease ($n = 4$) and Parkinson's disease ($n = 11$) were infrequently reported and therefore not included in Fig. 4. Somatic comorbidities were reported much less frequently than comorbid psychiatric conditions and included hypertension ($n = 20$), diabetes ($n = 19$), joint diseases ($n = 19$) and ischemic heart disease ($n = 13$).

3.4. Resource use and costs

Over the 12-month follow-up period there were 7291 visits to specialised psychiatric or somatic outpatient care (for $n = 3461$ patients) and 506 inpatient episodes (for $n = 358$ patients). Of these, 7005 outpatient visits and 462 inpatient episodes were classified as GAD-related, i.e. visits or episodes recorded with a primary diagnosis of GAD. Table 2 shows resource use and associated direct costs presented by gender and age group (< 65 years and ≥ 65 years) for patients with primary GAD. The mean direct costs for all patients ($n = 3701$) were SEK 21,109 (total costs, SEK 78,135,460) and mean

Table 2
Resource use and total costs.

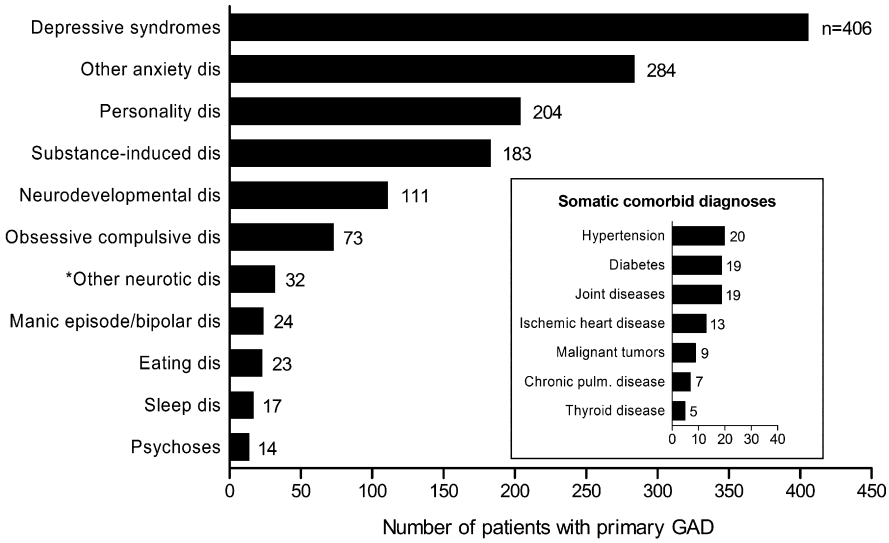
Cost are presented as mean costs in SEK	Females		Males		All patients ($n = 3701$)	
	< 65 years	≥ 65 years	< 65 years	≥ 65 years	Patients with observed costs	Sum of direct costs
Medication use	$n = 1873$	$n = 284$	$n = 1078$	$n = 117$	$n = 3352$	
Costs for medication dispensed	5270	6234	5841	4863	5520	18,502,683
No. of days supply	796	1144	830	1088	847	
No. of dispensed packages	25	43	26	38	27	
Inpatient care	$n = 166$	$n = 57$	$n = 100$	$n = 35$	$n = 358$	
Cost for inpatient care	112,879	72,454	65,684	101,546	92,156	32,990,582
GAD-related	106,138	64,855	59,500	99,461	85,886	30,746,884
No. of inpatient episodes	1.5	1.4	1.3	1.3	1.4	
GAD-related	1.4	1.3	1.2	1.2	1.3	
No. of days inpatient care	22	16	15	23	19	
GAD-related	21	15	13	23	18	
Outpatient care	$n = 1986$	$n = 250$	$n = 1124$	$n = 101$	$n = 3461$	
Cost for outpatient care	7748	6934	7727	8291	7698	26,642,194
GAD-related	7441	6534	7462	8077	7398	25,612,798
Number of outpatient visits	2.1	1.9	2.1	2.3	2.1	
GAD-related	2.0	1.8	2.1	2.2	2.0	
Direct costs	$n = 2105$	$n = 293$	$n = 1184$	$n = 119$	$n = 3701$	
All	20,895	26,051	18,203	41,690	21,109	78,135,460
GAD-related	20,081	24,230	17,424	40,890	20,231	74,862,365

Data are presented only for patients with observed resource use; all values are mean (where n: number of patients with observed costs > 0), apart from the final column which gives the total resource cost.
n: number of subjects.
All direct costs: outpatient visits, inpatient episodes, and medication supply.
Visits/episodes recorded with a primary diagnosis of GAD were classified as GAD-related.
Exchange rate for December 2011 was 1 EUR = 9.02 SEK. Costs presented are from 2008 and the inflation from 2008 to 2011 was 3.6%.

Table 3
Number of pharmacological categories prescribed to patients that received medication ($n = 3352$) by gender and age.

No. of pharmacological categories	Females, n (%)		Males, n (%)	
	< 65 years	≥ 65 years	< 65 years	≥ 65 years
≥ 1	1873 (100)	284 (100)	1078 (100)	117 (100)
≥ 2	1434 (77)	263 (93)	846 (78)	103 (88)
≥ 3	968 (52)	221 (78)	573 (53)	82 (70)
≥ 4	588 (31)	163 (57)	357 (33)	58 (50)
≥ 5	307 (16)	93 (33)	187 (17)	34 (29)

n: number of subjects; %: percentage of the total study population.



*Other neurotic disorders, including dissociative and somatoform
Abbreviation: dis=disorder

Fig. 4. Absolute number of subjects with common additional ICD-10 psychiatric comorbidities and somatic comorbidities (inset) in patients diagnosed with primary GAD. n: number of subjects.

GAD-related direct costs were SEK 20,231 (total costs, SEK 74,862,365). Thus, GAD-related direct costs accounted for 96% of all mean direct costs.

The mean duration of hospitalisation was 19 days in total (GAD-related duration, 18 days) over the course of 1 year for the 358 patients that received inpatient care. The mean number of recorded visits to specialised outpatient care over the 12-month follow-up period (for $n = 3461$ patients) was 2.1 for all outpatient visits (2.0 for GAD-related visits). Overall, the mean cost of hospitalisation for patients with inpatient visits was high (SEK 922,156; $n = 358$) in relation to medication (SEK 5520; $n = 3352$) and outpatient costs (SEK 71,698; $n = 3461$). Elderly women (≥ 65 years) had higher mean medication costs (SEK 6234; $n = 284$) than younger women (SEK 5270; $n = 1873$), whereas elderly men had lower medication costs (SEK 4863; $n = 117$) than younger men (SEK 5841; $n = 1078$) (Table 2). Hospitalisation costs were highest for younger women (SEK 112,879; $n = 166$) and elderly male patients (SEK 101,546; $n = 35$).

Patients with secondary diagnoses, i.e. comorbidity, had higher mean direct costs than patients without comorbidity. Medication costs were SEK 6691 ($n = 1152$) and SEK 4906 ($n = 2200$), hospitalisation costs SEK 110,623 ($n = 212$) and SEK 65,334 ($n = 146$), and outpatient costs SEK 8512 ($n = 1112$) and SEK 7312 ($n = 2349$) for patients with and without secondary diagnoses, respectively.

3.5. Logistic regression

Multivariate logistic regression analysis revealed that the odds for use of SSRI or SNRI monotherapy declined with increasing age per year (OR, 0.962; 95% CI, 0.956–0.969; $P < 0.001$) and the presence of one or more additional diagnoses (OR, 0.60; 95% CI, 0.48–0.84; $P < 0.001$). Gender had no effect on SSRI/SNRI monotherapy use. The use of anxiolytic monotherapy increased significantly with age per year (OR, 1.025; 95% CI, 1.012–1.038; $P < 0.001$) but was unaffected by gender and presence of secondary diagnoses. The probability for (any) therapy with antipsychotics increased with age (OR, 1.016; 95% CI, 1.010–1.022; $P < 0.001$) and additional diagnoses (OR, 1.74; 95% CI, 1.42–2.14; $P < 0.001$).

4. Discussion

Patients in specialist care registered with a recorded primary GAD diagnosis in Sweden in 2006 were associated with high 12-month hospitalisation costs compared to patients with any registered diagnosis, especially in younger females and elderly males and patients with comorbidities [45]. The number of hospitalisations per patient was slightly lower compared to the general Swedish population. In 2006, 10% of all Swedish citizens were hospitalised with a mean of 1.6 episodes per patient [45], while 9.7% of GAD patients were hospitalised with a mean of 1.4 episodes per patient. The difference in number of episodes could be explained by the fact that only 11% of the study population was more than 65 years of age, which was lower than the corresponding proportion for the general Swedish population (17.4%). These figures suggest that the rate of hospitalisation was somewhat higher for the typical GAD patient compared to the average Swedish citizen when data are adjusted for age.

An important finding was that patients with a recorded primary GAD diagnosis were prescribed large amounts of psychoactive medications during the 12-month follow-up period. They received maintenance psychoactive medications recommended in current practice guidelines (SSRIs or SNRIs) in 73% of cases; yet, polypharmacy was extremely common and a substantial proportion of patients received additional benzodiazepine-anxiolytics, antihistamines and hypnotics, the use of which was particularly high in elderly patients.

Approximately one-third of patients had at least one secondary comorbid diagnosis and the rate of psychiatric comorbidity was high. However, this figure is substantially lower compared to other reports [25,37] and it is likely that the true prevalence of comorbid symptoms is underestimated due to incompleteness of diagnostics of secondary diagnosis in the National Patient Register. Another important factor contributing to the low comorbidity rate presented here is that the proportion of comorbid patients is only captured during the course of 1 year and lifetime comorbidity in GAD is not captured. With respect to costs, we found that patients with comorbid diagnoses were associated with higher direct costs compared to GAD patients without comorbid diagnoses. This finding is similar to previously reported studies where the presence of a comorbid diagnosis was correlated with increased direct costs compared to costs in patients without a comorbid diagnosis [19,40]. Depressive syndromes were the most commonly reported secondary diagnoses, consistent with many other studies reporting a frequent co-occurrence of GAD and depression [11,22,23,47]. The fairly high rate of comorbid neurodevelopmental conditions in GAD was an unexpected finding that warrants further exploration. In our study, somatic comorbidities were reported less frequently than were comorbid psychiatric conditions, probably as such disorders were managed in primary care.

4.1. Resource use and costs

Total direct costs and resource use for GAD patients over the 12-month follow-up period were calculated in this study. Mean direct costs (which included costs for medication, outpatient and inpatient care) were high and consistent with the high rate of specialist care utilisation previously observed in GAD, particularly in patients with a comorbid condition [21,40,48]. Total direct costs in our study were similar to those previously reported [19]. Medication costs were relatively high compared to other direct costs and were highest in patients with comorbidities and women aged 65 years and older, consistent with the high consumption of medication and polypharmacy rate in these subgroups. The most expensive medications used were atypical antipsychotics; although these drugs were used in only 12% of patients, they are several times more expensive than other psychoactive treatments.

On the other hand, outpatient costs were low in relation to other direct costs for this patient population. The mean number of visits to outpatient care was 2.0 per patient per year during the study period 2006–2007, whereas the corresponding value for any patient in the register during 2006 was 2.9 visits (data not shown). This may be partly due to underreporting of outpatient visits in private psychiatric care and the absence of recorded visits in primary care (see study limitations below). Another tentative explanation is that patients were initially referred from primary care and then returned after one or two visits, i.e. following initiation of treatment or improvement of previous therapy. Data on primary care visits are not available for this Swedish patient population, although studies in other countries have shown that the use of primary care services by GAD patients is generally very high [8,46].

Recording of inpatient care episodes in the National Patient Register is compulsory for physicians and care providers. Although only approximately 10% of GAD patients were hospitalised during the study, mean hospitalisation costs were high in relation to medication costs and outpatient costs in specialised care. The mean number of hospitalisation days for patients with any diagnosis in the register was 9.5 days during 2006 (data not shown), compared with 19 days for the current study population during the 12-month follow-up period. Younger women had the

highest hospitalisation costs; the reason for this is unknown and warrants further study. Patients with comorbidity also had high hospitalisation costs, presumably as the rate of admission for co-existing conditions is higher. Conceivably, early treatment initiation along with the availability of multiple treatment options to optimise individual pharmacological management may reduce the number or duration of inpatient episodes, thereby leading to cost offsets.

4.2. Medication treatment patterns

In accordance with both Swedish and international practice guidelines [6,30,42], the majority of patients were treated with SSRIs or SNRIs. Although treatment recommendations list SNRIs as a first-line therapy for GAD, interestingly, SNRIs were prescribed to fewer patients compared with benzodiazepine-anxiolytics, antihistamines and hypnotics. Furthermore, the SNRI group included mirtazapine and mianserin; these agents, which modulate synaptic turnover of noradrenaline and serotonin, together accounted for almost half of the prescriptions in this pharmacological category (data not shown), despite the lack of controlled data to support their use in GAD.

Many national bodies advocate the short-term use of adjunctive benzodiazepines for immediate symptomatic relief in the early phases of treatment with SSRIs or other antidepressants, as well as for episodes of symptom exacerbation. However, it is generally recommended that patients should not be treated with benzodiazepine-anxiolytics for more than a few weeks because of the risk of tolerance and memory impairment [3]. According to the WFSBP, long-term benzodiazepine use should be reserved for patients who have failed other drugs or psychotherapy. In our study benzodiazepine-anxiolytics were prescribed to almost half of all patients and their use was widespread among the elderly, suggesting that SSRIs/SNRIs alone have insufficient anxiolytic and hypnotic efficacy in this group. Our finding of an overall 47% use of benzodiazepine-anxiolytics is much higher than in a previous report [26] (33%) that examined the use of benzodiazepine-anxiolytics in patients with major depressive disorder. Consistent with our findings, the use of benzodiazepine-anxiolytics and hypnotics increased with age. Moreover, the results are somewhat disturbing given that benzodiazepines are associated with increased cognitive impairment and higher frequency of falls in older patients [12,27]. Interestingly, the most frequently prescribed benzodiazepine-anxiolytics in our study was oxazepam (data not shown), which is not mentioned in either WFSBP or Swedish recommendations [6,42].

Although antihistamines are not indicated for GAD, these agents were prescribed to approximately one-half of patients during the 12-month study period. Antihistamines are sometimes used as daytime anxiolytics, but because of their sedative effects they are mainly prescribed for use at night to facilitate sleep, although there is no evidence for their utility in this regard [43]. Atypical antipsychotics, which were dispensed to 12% of the total population and to approximately 20% of elderly women, have potentially serious side effects such as metabolic syndrome and rare lethal arrhythmias, and are currently not approved for primary GAD treatment. Considering the low observed rate of comorbid psychosis, the results suggest that either antipsychotics were used in non-psychotic patients with severe anxiety symptoms, or reporting of secondary diagnoses by physicians was incomplete. It is worth noting that the antipsychotic agent quetiapine (although not approved for GAD) is listed in WFSBP GAD treatment recommendations based on the results of short-term Phase 3 studies [6]. Atypical antipsychotic medications are also used in bipolar disorder and schizophrenia, but the number of patients with these conditions in the present study was low: 24 patients were diagnosed with manic episodes or bipolar disorder, and 11 had schizophrenia-related diagnoses.

There was a high rate of polypharmacy with psychoactive medications during the 12-month follow-up period, particularly among the elderly. A large proportion of the study group (71%) received drugs from two or more pharmacological categories, and approximately 80% of patients on SSRIs or SNRIs were prescribed additional psychoactive medications. This suggests that SSRI/SNRIs alone are not sufficient for the treatment of GAD patients in specialised care. Published data on the use of polypharmacy in the specialised care setting are currently lacking, but one survey of treatment patterns in office-based psychiatry practices in the United States revealed an increase in the prescription of antidepressant and sedative hypnotic combinations for patients with anxiety between 1996 and 2006 [28]. Although there is currently no scientific rationale for the use of polypharmacy in GAD, the high occurrence of psychiatric comorbidity increases the need for combination therapies [31,32]. Indeed, previous cross-sectional analyses have found that the use of anxiolytics, hypnotics, tranquilizers and antidepressants is increased in GAD patients with comorbid psychiatric conditions [4,40].

In general, the rate of non-response to first-line pharmacological therapy with SSRIs/SNRIs in GAD is high and approximately 30–40% of cases are treatment-resistant in clinical trials [15,17,35]. Further, these agents have several other important limitations including a delay before the onset of symptom relief (typically 2 to 4 weeks), partial remission, risk of relapse and intolerable side effects [20]. The rate of non-response to SSRIs and SNRIs highlights the need for multiple treatment options and in our study probably contributed to the long-term use of benzodiazepines and other drugs that are not specifically indicated for GAD, such as antihistamines and antipsychotics. It is therefore important that alternative, effective therapeutic options exist for patients failing treatment with SSRIs/SNRIs. One treatment algorithm discussed the use of augmentation strategies (e.g. with atypical antipsychotics) for partial response or switching strategies for partial or non-response in patients with general symptom persistence [16]. However, the authors acknowledged that long-term controlled trials are currently lacking and there is little evidence-based guidance on the best management strategy for these patients.

Although the majority of GAD patients in the present study were treated pharmacologically, approximately 10% ($n = 349$ of 3701) did not receive any psychoactive medications. Alternative treatments such as cognitive behavioural therapy are described in clinical guidelines and maybe a useful augmentation strategy to pharmacological therapies [41]. However, the extent to which psychosocial interventions are employed in clinical practice, either alone or in combination with drug therapy, is currently unknown. In a study of adult patients in Swedish primary care in 2001, psychotherapy was reported in almost one-half of cases with anxiety and/or depression [2].

4.3. Limitations

The results of this study should be interpreted in the context of several limitations.

First, the number of GAD cases in Sweden during 2006 is underestimated, and therefore the total direct costs associated with the disease are likely to be underestimated. Primary care visits are not recorded in Swedish national registers and the analysis included only those patients treated in specialised care. Outpatient visits among private care providers are also likely to be underreported and, in addition, GAD may be diagnosed using criteria other than the ICD-10 classification (e.g. DSM-IV) which would also lead to underestimation of the number of GAD cases and total direct costs. Also, there was no information on the history

of GAD prior to the study period. The number of subjects identified with a primary diagnosis of GAD (3701) comprises less than 0.1% of the total Swedish population. This figure should not be interpreted as an estimate of GAD prevalence in Sweden because it is likely to be biased, i.e. underestimated, for reasons provided above and because many patients may not have GAD as a primary diagnosis. Second, estimates of psychiatric comorbidity are based only on registered diagnoses, so as with primary GAD, are likely to be underestimated; there may also be differences or variability in diagnostic accuracy for comorbid conditions. Third, in-hospital medication use is not recorded in the Swedish Prescribed Drug register. Thus, medication costs are likely underestimated in patients receiving inpatient care (drug costs were included in the cost per bed-day). Fourth, it is likely that patients in this study had a stronger need for medical treatment and higher disease burden compared to patients in primary care (i.e. patient selection bias may exist versus the general GAD population); however, the validity of the diagnosis is probably higher in a specialty setting. Fifth, the study period was limited to 12 months only. Therefore, while this study provides a good estimate of outpatient and inpatient care, estimates of treatment patterns are limited because fluctuations may occur over a longer period of time. Ideally, a period of 5 years would be more appropriate to follow individual changes in medication use. Sixth, although all relevant costs should be considered in an explorative study, indirect costs such as sick leave and family burden cannot be calculated from the registers used in this study. We have therefore included direct costs only (medical costs for dispensed medications and costs for inpatient and outpatient care, where data are nearly 100% for inpatient care). Previous studies have reported that indirect costs are in line with the cost for hospitalisation [19]. Finally, this study did not include a matched population without a GAD diagnosis meaning that comparative analyses between patients with GAD and without GAD were not possible.

5. Conclusions

The high rate of polypharmacy, significant psychiatric comorbidity and widespread use of benzodiazepine-anxiolytics, hypnotics and medications that are not indicated for GAD suggest that the GAD disease burden is high and highlight the need for multiple treatment options. Total direct costs associated with the disease were high but still likely to be underestimated. Indeed, the present findings should be seen in the light of important study limitations, such as underestimation of costs due to inclusion of patients in specialized care only and underreporting of outpatient visits among private care providers. Furthermore, it is likely that patients included in this study had a stronger need for medical treatment and higher disease burden compared to patients in primary care. Future studies may benefit from a longer follow-up period of resource use which enables year-to-year comparisons and a more comprehensive investigation of the patterns concerning medication use.

Disclosure of interest

R.S.: employee of Pfizer Sweden.

E.A: former employee of Pfizer Sweden.

J.K.: consultant in statistics for Pfizer in this project and several other pharmaceutical, biotech and medtech companies. No ownership or other connections to Pfizer.

C.A.: employed by the Karolinska Institutet. Received lecture honoraria in 2009 and 2010 from Eli Lilly Sweden, AstraZeneca Sweden and Pfizer Sweden, and honoraria as an advisor to Pfizer Sweden.

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