Initiation, execution and discontinuation of antidepressant therapy:

considerations and decisions of patients

Katja van Geffen · **2008**

Cover: Quotes that represent experiences and beliefs of antidepressant users shortly after initiating treatment. The quotes were adapted from the interview study described in Chapter 3.2.
Design and lay-out: Marjolein Smithuis, Communications and Design, Faculty of Science, Utrecht University

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Starten, uitvoeren en stoppen van een behandeling met antidepressiva:
overwegingen en beslissingen van patiënten
(met een samenvatting in het Nederlands)

Proefschrift

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1 Introduction

Depression and anxiety are common in Western society and can have a huge impact on a person's life. Depression has been determined by the World Health Organisation as one of the main causes of the global disease burden (1). Next to psychotherapy, antidepressants have shown to be effective in the treatment of depression and anxiety by reducing symptoms, as well as the risk of relapse and recurrence (2,3). Yet, several obstacles have been acknowledged in the process of adequate diagnosis and treatment of patients with these diseases: underrecognition of the health problem by the patient, underconsultation among patients who need treatment, failure to recognise and diagnose the problem by the physician, failure to prescribe drug treatment for those who need so, and eventually, on the part of the patient, not taking the drug as instructed. Many patients suffering from depression and anxiety do not consult their physician (4,5), and around one-half of those who consult the physician are not recognised as depressed and do not receive treatment (6-10). Thereupon, many of those who have prescribed antidepressant treatment do not take their medicine in accordance with the instructions (11-13).

This brings us to the basis of this thesis – the course of drug taking. The course of drug taking can be described as a sequence of actions. The sequence starts when patients receive a prescription from a physician for a new course of drug treatment, and ends with discontinuation of drug use. For the quantitative assessment of how patients take their prescribed medicines, Urquhart & Vrijens suggested to consider separate phases within the course of drug taking (14). Based upon their conceptual framework, we suggest the course of drug taking to consist of three phases, as visualised in Figure 1: initiation of drug treatment, execution of the drug regimen, and eventually discontinuation. The initiation phase includes the receipt of a prescription for a new course of treatment, followed by filling the prescription at the pharmacy and initiation of drug taking. The execution phase refers to the events and issues surrounding the execution of the drug regimen itself and to the rhythm of drug taking, and the discontinuation phase refers to the causes and consequences of the termination of drug taking. This framework can be considered as a taxonomic refinement of the generally used terms adherence and compliance, which cover any type of deviations patients make from professional instructions.

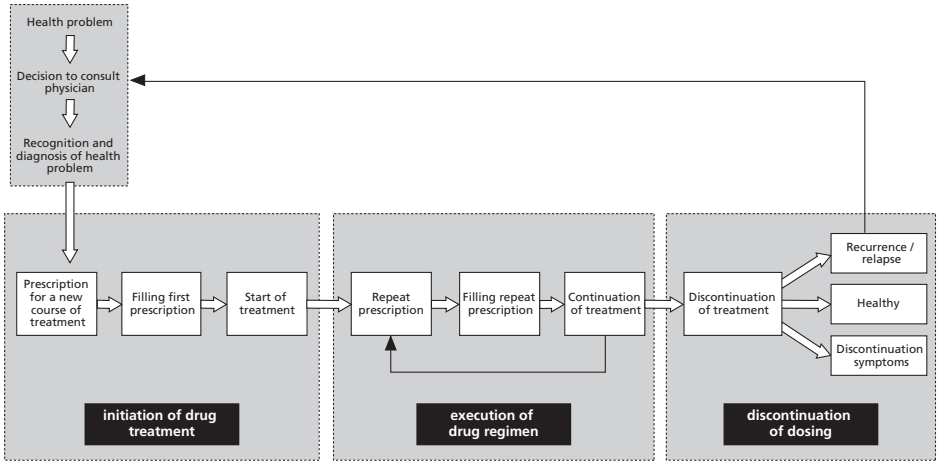

Figure 1 **Course of antidepressant taking – initiation, execution and discontinuation**

Initiation and discontinuation are dichotomous, while execution is a continuous process, that is the extent to which the patient's actual dosing corresponds to the prescribed dosing regimen. The time between the first and last taken dose is called persistence (14).

Throughout the course of antidepressant taking patients are constantly making decisions about their health and whether or not to comply with the treatment plan (15). Most likely problems arising during the course of treatment – and the factors concerned – vary within and between persons. Therefore, we consider it important to unravel the key decisional events, in order to understand why patients make certain decisions on certain points in time. First, when receiving the prescription from a physician, the patient decides whether to present the prescription at the pharmacy for dispensing. In general, research has found that up to 20% of patients fail to fill their prescription at the pharmacy (16-18). Yet, the number of patients who do not fill a prescription for a new course of antidepressant treatment is unknown. Further, having filled the prescription, the patient reassesses his/her health and the need to start medicine use in the light of the information received. Of all patients who get an antidepressant dispensed at the pharmacy, up to 38% fill only a single prescription (10,19-21). These patients have either not started antidepressant use, or used the antidepressant just for a couple of days. Antidepressant side effects may occur immediately after start, while it usually takes some weeks before patients experience improvement of the psychiatric symptoms (11). After the first weeks, most of the initial side effects usually subside and patients gradually start feeling better. Longer-term side effects, that have a much more insidious onset, such as weight gain, sexual dysfunction,

sleep disturbances and apathy, can bother patients also later on during treatment. Partial non-adherence and dosing lapses often occur during execution of the drug regimen (22,23). Bambauer et al. reported delayed refills in 75% of patients starting treatment with antidepressants, with an average of 40% of days without dispensed antidepressants being taken (22). A study in long-term users found that 73% of patients occasionally miss a complete day of dosing and 29% occasionally miss two or more consecutive days (23). In the Netherlands it is common practice to dispense a 14 day supply for new prescriptions, and subsequent prescriptions are usually for a 30 day supply. Consequently, every couple of weeks patients have to decide whether they want to continue drug taking, which entails contacting the physician for a next prescription and have it dispensed at the pharmacy. Many patients decide to discontinue treatment with antidepressants before the minimum six months' duration recommended for treatment of depression and anxiety (3,24,25). About one-third of patients discontinue treatment within one month after start, between one-third and half within three months, and as many as half of patients stop taking antidepressants in the first six months of treatment (20,26-30). The decision to discontinue treatment can be taken on advice or in consultation with the physician. Yet, two studies showed that a considerable number of patients, 24% and 63% respectively, do not inform their physician when they stop taking the antidepressant (27,29). When antidepressant treatment is terminated or interrupted discontinuation or withdrawal symptoms can occur (31-33). Discontinuation symptoms are usually mild and transient but in some patients they can be severe and longer lasting. Discontinuation symptoms can cause significant morbidity, have adverse effects on patients' quality of life and may lead to unnecessary renewed antidepressant use (31-33). As a consequence, tapering antidepressant therapy as opposed to abrupt discontinuation, has been recommended as part of routine practice in several guidelines and in literature (3,24,25). However, there are no observational or experimental direct comparative studies that support this, and it is unclear how patients discontinue antidepressant treatment in daily practice.

Objective of the thesis

Observational studies have revealed important quantitative information on the course of antidepressant drug taking in daily practice. Few studies, however, have provided qualitative information explaining patients' behaviour towards antidepressant use. In fact, up to now little is known about patients' experiences and views on antidepressant taking and how these relate to decisive moments in the course of drug taking. Patients' perspectives are increasingly acknowledged

as important, and knowledge about patients' evaluations of treatment can help to understand why patients make certain decisions (34).
The objective of this thesis is to explore the course of taking antidepressants from a patient's perspective, in order to understand what patients take into consideration when they decide to deviate from professional instructions, from the moment they received a first-time antidepressant prescription.

Outline of the thesis

Research in this thesis is build upon the previously explained three phases within the course of drug taking: initiation, execution and discontinuation.
Chapter 2 includes four studies exploring the initiation phase of antidepressant therapy. So far, no studies have focused on patients who consult their physician about a health problem and receive a prescription for a new antidepressant course, but don't initiate treatment. Chapters 2.1 and 2.2 explore the incidence and characteristics of patients not initiating antidepressant treatment. The patients in question are those who receive a prescription for a new antidepressant course from their physician but do not fill it at the pharmacy, and patient who fill only a single antidepressant prescription. Also, Chapter 2.2 describes the reasons for not filling a second prescription. Providing information is considered important in order to increase adherence, and is increasingly seen as a requisite to support patients' involvement in treatment decisions. The studies in Chapters 2.3 and 2.4 focus on patients' perceptions of the information received, patients' information needs, and the potential role of the pharmacy as provider of information.
Chapter 3 concentrates on the execution phase of antidepressant therapy. Three studies are presented, which investigate the patients' experiences with treatment and their attitudes and beliefs towards antidepressants in response to the experiences of taking them. Chapter 3.1 presents a study in which patients are followed during six months after filling a prescription for a new course of antidepressant treatment. Patients' characteristics, severity of symptoms, attitudes and beliefs towards the illness and antidepressant are assessed in relation to the duration of use. Chapter 3.2 describes a qualitative study that explored how experiences and beliefs of users of selective serotonin-reuptake inhibitors influence the decision to continue or discontinue treatment. Chapter 3.3 describes patients' experiences with antidepressant taking reported by means of an internet-based medicine reporting system, and the relevance of these experiences to patients. In addition, the nature of side effects reported by patients and healthcare professionals is compared to assess whether events found bothersome or relevant by patients differ from those that healthcare professionals find relevant.

In Chapter 4, two studies are presented that focus on the problems patients experience with discontinuation of antidepressant treatment. It is unclear whether patients perceive discontinuation of antidepressants as a problem. Chapter 4.1 presents a study using information from a national telephone medicines information service call register, in order to assess whether concerns and problems experienced with drug discontinuation occur more frequently in patients using antidepressants, than in patients using benzodiazepines, antipsychotics or non-psychiatric medication. Also, it is unknown how patients discontinue antidepressant treatment in daily practice, and whether abrupt discontinuation causes adverse effects. Chapter 4.2 describes how patients discontinue SSRI treatment in clinical practice, and compares the effect of tapering with that of abrupt discontinuation on the occurrence of discontinuation symptoms.
Finally, in Chapter 5, the results of these studies are discussed in a broader context. Implications for research and clinical practice, and recommendations for physicians and pharmacists on improving care for patients starting treatment with antidepressants are considered.

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2 Initiation of antidepressant therapy

2.1 Initiation of antidepressant therapy: do patients follow the general practitioner's prescription?

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Abstract

Introduction

Initiation of drug treatment has hardly been addressed in research. Often overlooked is the question whether patients actually start drug taking after having received a first prescription. The aim of this study was (1) to determine the incidence of patients who decline the first-time antidepressant prescription, and (2) to identify associated patient characteristics.

Methods

Data were obtained by linkage of a Dutch general practice registration database to a dispensing registration database. Subject to the study were patients who received a first-time prescription for a second-generation antidepressant (SSRI, venlafaxine, mirtazapine) in the year 2001. Three mutually exclusive patient groups were identified: (1) patients who received a prescription but did not fill that prescription at the pharmacy (nonfillers), (2) patients who filled only a single prescription (single Rx-fillers), and (3) patients who filled at least two consecutive antidepressant prescriptions (initiators). For analysis, nonfillers and single Rx-fillers were combined into a group of decliners.

Results

Of all 965 patients receiving a first-time prescription for a second-generation antidepressant in general practice, 41 (4.2%) did not fill that prescription at the pharmacy (nonfillers) and 229 (23.7%) filled only a single prescription (single Rx-fillers). Patients who consulted their general practitioner (GP) for a non-specific indication, rather than for depression, anxiety, panic or obsessive compulsive disorder, were almost three times more likely (OR 2.7, 95% CI 1.8 to 3.9) to decline treatment. Further, the risk of declining was almost five times higher (OR 4.8, 95% CI 2.1 to 11.3) in non-western immigrants, and almost two times higher (OR 1.8, 95% CI 1.2 to 2.8) in patients over 60 years of age.

Conclusion

Over one in four patients who receive a first-time antidepressant prescription decline treatment; they either do not initiate drug taking or do not persist antidepressant use for longer than two weeks. GPs could be more aware of the possibility of patients declining their first-time prescription. They need to engage with patients' priorities and concerns, and could ask patients whether they believe an antidepressant would be helpful in treating their symptoms.

Introduction

Initiation of drug taking is a complicated process in itself, as it involves patients and physicians making consecutive decisions. When faced with a health concern, the patient needs to recognise it as a problem and to decide whether to consult a physician. Thereupon, the physician must be able to recognise and diagnose the patient's health problem and may propose treatment, including drug treatment. If the physician-patient encounter results in a prescription for drug treatment, the patient subsequently has to decide whether to present the prescription at the pharmacy for dispensing. Having filled the prescription, the patient has to initiate treatment by taking the first tablet. And finally, the patient has to decide to persist in drug taking. Although this factual sequence of actions leads to a simple dichotomous decision to initiate or not to initiate drug treatment, it in fact involves a complex cognitive process taking many considerations into account. The decision to initiate drug taking is influenced by the way in which patients evaluate their personal need for medication relative to their concerns about potential negative effects of taking it (1,2). Patients evaluate whether the physician's advice to start drug taking makes common sense in the light of their own understanding and beliefs about the illness and treatment.

Numerous studies have focused on patients who discontinue antidepressant use before the recommended duration of treatment. Between one-third and half of patients stop taking the antidepressant within three months, and less than half continue to take their antidepressant medication for a full six months (3-8). Multiple factors have been hypothesized to be predictors of early discontinuation, including sociodemographic, disease and treatment-related factors (4,8-13). However, initiation of antidepressant drug treatment has hardly been addressed in research. Often overlooked is the question whether the patient collects the drug at the pharmacy, and whether the patient actually starts drug taking. It has been found that overall (i.e. all prescriptions and all therapeutic groups), between 7 and 20% of patients fail to redeem their prescription at the pharmacy (14-16). These studies, however, do not provide insight into the nonfilling of antidepressant prescriptions, and first-time prescriptions in particular. Furthermore, it has been shown that of all patients having an antidepressant dispensed at the pharmacy, up to 38% fill only a single prescription (6,17-20). Of those filling only a single antidepressant prescription, one-third did never initiate drug taking (3,20).

To date, there have been no studies published that specifically explored the extent and determinants of declining the prescription for a new antidepressant treatment. The aim of this study therefore was (1) to determine the incidence of patients who do not fill the first-time antidepressant prescription or fill only

a single antidepressant prescription at the pharmacy, and (2) to identify patient characteristics associated therewith.

Methods

Study setting

Data for this study were obtained by linkage of routine registration data collected in general practice to a pharmacy dispensing registration database. In the Netherlands every individual is listed in a general practice. General practice data were obtained from the Second Dutch National Survey of General Practice (DNSGP-2), which was carried out in 2001 by the Netherlands Institute for Health Services Research (NIVEL) in cooperation with the National Institute for Public Health and the Environment (RIVM). The DNSGP-2 has been described in detail elsewhere (21). In short, 195 general practitioners (GPs) in 104 practices registered details for all physician-patient contacts, including prescriptions and referrals, during 12 months in a standardised way. GPs were trained during an intensive course on coding practices and problems by the LINH (Dutch Information Network GPs). The GPs registered and coded all health problems presented within a consultation according to the International Classification of Primary Care, ICPC (22). Furthermore, 76.5% of the total source population responded to a sociodemographic census with questions on health insurance, educational level, employment status and perceived health. Most census data were collected in 2000. Pharmacy dispensing data were collected by the Foundation for Pharmaceutical Statistics (SFK). Medication histories of Dutch pharmacies are virtually complete because almost all patients fill their prescriptions, from GPs and medical specialists, at a single pharmacy. Data from both sources were linked by researchers from Utrecht University (23). In short, 110,102 patients from 83 general practices participating in DNSGP-2 were identified in 112 pharmacies who delivered data to SFK. The SFK data include dispensing data for the patients from 1999 to 2003. Linking was based on the patient's gender, year of birth, postal code and prescription characteristics. Prescription characteristics were used in the linking process because the other three linking keys did not provide unique matches for all patients. Linking GP prescribing and pharmacy dispensing data enables to distinguish between drug prescribing and dispensing, which offers the possibility to assess whether prescriptions from the GP are collected at the pharmacy.

The study was carried out according to Dutch legislation on privacy. The privacy regulation was approved by the Dutch Data Protection Authority. According to Dutch legislation, obtaining informed consent is not obligatory for observational studies.

Study population

Subject to the study were patients aged over 18 years, who received a first-time prescription for a second-generation antidepressant (selective serotonin-reuptake inhibitor (SSRI), venlafaxine or mirtazapine) from the GP in the year 2001. The date of the first antidepressant prescription that the patient received, as registered by the GP, was defined as the prescription date. First-time use was defined as having no antidepressant prescriptions dispensed, according to pharmacy dispensing data, in the six months before the prescription date of the study antidepressant. In the Netherlands, guidelines call for a 14 day supply for new prescriptions and subsequent prescriptions are usually for a 30 day supply.

Outcomes

Three mutually exclusive outcomes were identified: (1) patients who received an antidepressant prescription from the GP, but did not fill that prescription at the pharmacy (nonfillers), (2) patients who filled only a single antidepressant prescription at the pharmacy (single Rx-fillers), and (3) patients who filled at least two consecutive antidepressant prescriptions (initiators). Patients were defined as nonfiller when the first prescription was not dispensed at the pharmacy within 30 days of the prescription date. Patients were defined as single Rx-fillers when the first prescription was dispensed at the pharmacy, but not followed by a second antidepressant dispensing within 30 days after the theoretical end date of the first prescription. All other patients were defined as initiators. The theoretical end date equals the dispensing date of the prescription plus the theoretical duration of drug use, the latter being calculated by dividing the number of units of dispensed drug by prescribed daily dose.

Determinants

To identify patient characteristics associated with declining the first-time antidepressant prescription three different types of determinants were explored: sociodemographic, health and morbidity, and medication related characteristics.

Sociodemographic characteristics

Next to age and gender, social status, ethnicity and living situation were included as socio-demographic characteristics. As indicators for social status we included educational level (none/primary school vs secondary school vs college/university), type of health insurance (public vs private) and employment status (employed or in school vs not employed or in school). Furthermore, first and second generation immigrants from non-western countries were compared to the combined population of western immigrants and the indigenous Dutch population. Finally, variables for living situation (living alone vs living with partner and/or children)

Table 1 Characteristics of patients who receive a first-time antidepressant prescription in general practice: nonfillers, single Rx-fillers and initiators

Measures	Decliners [a] n=270 (28.0%)		Initiators [d] n=695 (72.0%)	Decliners vs Initiators p-value [e]	Nonfillers vs Single Rx-fillers p-value [e]
	Nonfillers [b] n=41 (4.2%)	Single-Rx fillers [c] n=229 (23.7%)			
Sociodemographic characteristics					
Female gender (n,%)	35 (85.4)	151 (65.9)	471 (67.8)	0.74	0.01
Age (n, %)					
18-30	3 (7.3)	34 (14.8)	93 (13.4)	0.08	0.33
31-45	11 (26.8)	71 (31.0)	254 (36.5)		
46-60	12 (29.3)	67 (29.3)	212 (30.5)		
>60	15 (36.6)	57 (24.9)	136 (19.6)		
Educational level [f] (n,%)					
none/primary school	5 (20.0)	47 (31.1)	93 (19.4)	0.01	0.37
secondary school	15 (60.0)	86 (57.0)	294 (61.3)		
college/university	5 (20.0)	18 (11.9)	93 (19.4)		
Employed or in school [f] (n,%)	9 (34.6)	69 (46.6)	248 (51.3)	0.14	0.26
Non-western background [f] (n,%)	2 (7.7)	18 (11.8)	13 (2.6)	<0.001	0.54
Marital status [f] (n,%)					
unmarried	8 (30.8)	32 (21.2)	114 (23.3)	0.33	0.43
married/registered partnership	16 (61.5)	90 (59.6)	312 (63.8)		
divorced	1 (3.8)	9 (6.0)	27 (5.5)		
widowed	1 (3.8)	20 (13.2)	36 (7.4)		
Living together [f] (n,%)	21 (80.8)	114 (75.5)	398 (81.4)	0.14	0.56
Public health insurance (n,%)	30 (73.2	181 (79.0)	525 (75.5)	0.64	0.53
Health and morbidity related characteristics					
Specific indication for antidepressant: depression, anxiety, panic or OCD (n,%)	24 (58.5)	128 (55.9)	506 (72.8)	<0.001	0.75
Self-perceived health [f] (n,%)					
very poor/poor	0 (0)	20 (13.9)	30 (6.5)	0.06	0.02
moderate	13 (52.0)	41 (28.5)	140 (30.2)		
good/excellent	12 (48.0)	83 (57.6)	293 (63.3)		
Psychotherapeutic therapy (n,%)	6 (14.6)	27 (11.8)	79 (11.4)	0.71	0.61
Other chronic diseases (n,%)	15 (36.5)	63 (27.5)	180 (25.9)	0.35	0.24
Number of other chronic diseases (mean±SD)	0.5 (0.7)	0.4 (0.8)	0.4 (0.7)	0.21	0.67
Number of contacts with GP in previous 6 months (mean±SD)	5.1 (4.6)	5.1 (5.7)	4.8 (5.2)	0.44	0.99
Contact with GP within 28 days after prescription date (n,%)	25 (61.0)	107 (46.7)	487 (70.1)	<0.001	0.09
Medication characteristics					
Use of paroxetine (vs other antidepressants) (n,%)	17 (41.5)	113 (49.3)	387 (55.7)	0.04	0.35
Co-medication (n,%)					
benzodiazepines	14 (34.1)	89 (38.9)	279 (40.1)	0.57	0.57
antipsychotics and lithium	1 (2.4)	9 (3.9)	18 (2.6)	0.36	0.64
Number of co-medicines (mean±SD)	3.2 (2.9)	3.9 (4.1)	3.5 (3.8)	0.35	0.33

and marital status (unmarried vs married/registered partnership vs divorced vs widowed) were included.

Health and morbidity related characteristics

The physician-patient contact registration includes information on the health problem for which the patient consulted the GP during the study period in the year 2001. We assessed whether the patient visited the GP during this period due to specific indications for second-generation antidepressants: anxiety/panic disorder (P74), depression (P76), and obsessive compulsive disorder (OCD) / phobia (P79). These indications are the officially approved indications for the second-generation antidepressants in the Netherlands. The antidepressant drug users could have more than one indication registered in the contact file. If the patient did not visit the GP for any of the specific indications (P74, P76 or P79), the patient was considered having a non-specific indication for use, including, among others, feeling anxious (P01), depressive feelings (P03) and sleeping problems (P06). The presence of chronic disease and the total number of other chronic diseases for which the patient contacted the GP during six months before the prescription date, were also assessed. Furthermore, the total number of contacts the patient had with the GP during the six months prior to prescription date, and whether the patient consulted the GP within 28 days after the prescription date were investigated. Finally, a first referral to a psychotherapist during the study period, and information on self-perceived health (very poor/poor vs moderate vs good/excellent), were included.

Medication characteristics

Included as medication characteristics were type of prescribed antidepressant, any use of psychotropic co-medication (benzodiazepines or antipsychotics), and the number of other co-medication during six months before the prescription date. Co-medication variables were obtained from the pharmacy dispensing registration database.

Data analysis

For the analysis, nonfillers and single Rx-fillers, were combined into a group of decliners; that is patients who did not fill the prescription, patients who did fill the prescription but did not start drug taking, and patients who filled the prescription but did not persist antidepressant use for longer than two weeks. Chi-square test (for the categorical measures) and Independent samples t test (for the continuous measures) were used to compare the characteristics between decliners and initiators,

a Decliners: patients who do not fill or only fill a single prescription at the pharmacy (the combined group of nonfillers and single Rx-fillers)
b Nonfillers: patients who do not fill their first-time antidepressant prescription at the pharmacy
c Single Rx-fillers: patients who do only fill a single antidepressant prescription at the pharmacy
d Initiators: patients who fill at least 2 consecutive antidepressant prescriptions at the pharmacy
e Chi-square test was used to compare categorical measures; Independent samples t test was used to compare the continues measures
f Variables obtained from the patient census which included questions regarding education, personal situation and self-perceived health. Of all patients included in the study, 671 (69.5%) responded to the census

and between nonfillers and single Rx-fillers. To control for covariates and identify the risk factors for declining a first-time antidepressant prescription, multivariate logistics regression analysis was performed in the group of patients for which consultation, dispensing and patient census data were available (n=671). Covariates significant in the univariate analysis at a p-value less than 0.1, including patient sex, were included in the logistic regression model. Data were analysed using SPSS version 14.0.

Results

Of all 965 patients receiving a first-time prescription for a second-generation antidepressant in general practice, 41 (4.2%) did not fill that prescription at the pharmacy (nonfillers) and 229 (23.7%) filled only a single prescription (single Rx-fillers). The mean (±SD) age of all patients was 48.5 (±16.8) years and 657 (68.1%) were female. Of all patients, 517 (53.6%) were prescribed paroxetine, 98 (10.2%) fluvoxamine, 87 (9.0%) mirtazapine, 86 (8.9%) fluoxetine, 74 (7.7%) citalopram, 74 (7.7%) venlafaxine, and 29 (3.0%) were prescribed sertraline.

Table 1 shows the sociodemographic, health and morbidity related, and medication characteristics for the nonfillers, single Rx-fillers and initiators. Nonfillers and single Rx-fillers were combined into a group of decliners, and compared with the group of initiators. For 671 patients (69.5% of all), census data were available.

The results of the multivariate logistic regression analysis for the association between patient characteristics and declining the prescription are shown in Table 2. Patients who consulted their GP for a non-specific indication, rather than for depression, anxiety, panic or OCD, were almost three times more likely (OR 2.67, 95% CI 1.82-3.91) to decline the antidepressant prescription. In half of the cases the decliners were not diagnosed with either depression, anxiety, panic or OCD; 24.4% consulted the GP for the indications feeling depressed, feeling anxious or sleeping problems, and 19.3% for other non-specific indications, such as fatigue, weight loss and relation problems. Of all patients diagnosed with the indications feeling depressed, feeling anxious or sleeping problems, 33.8% declined treatment, and of all patients considered having any other non-specific indications, 46.4% did so. In addition, the risk of declining treatment was almost five times higher (OR 4.80, 95% CI 2.05-11.3) in non-western immigrants, and almost two times higher (OR 1.81, 95% CI 1.18-2.78) in patients over 60 years of age. Overall, the decliners were less likely to consult the GP within four weeks after the prescription date, compared to the initiators. However, comparing the nonfillers and single Rx-fillers, there was a trend that nonfillers were more likely to consult the GP within four weeks after the prescription date.

Table 2 Characteristics associated with declining the general practitioners' prescription: patients who do not fill the first-time antidepressant prescription or fill only a single antidepressant prescription at the pharmacy [a]

	Crude OR	95% CI	Adjusted OR [b]	95% CI
Non-specific indication for prescribing antidepressant (rc. [c] indication of depression, anxiety, panic or OCD)	2.61	1.80-3.78	2.67	1.82-3.91
Non-western immigrants (rc. western origin)	3.67	1.63-8.25	4.80	2.05-11.3
Age above 60 (rc. all other ages)	1.75	1.17-2.63	1.81	1.18-2.78
Female (rc. male)	0.96	0.65-1.42	0.92	0.61-1.39
Educational level precollege (rc. college/university)	1.53	0.93-2.52	1.40	0.83-2.36
Self-rated health poor/moderate (rc. good/excellent)	1.33	0.93-1.91	1.11	0.76-1.63
Paroxetine prescribed (rc. other antidepressants)	0.72	0.51-1.03	0.78	0.53-1.13

a Multivariate logistics regression analysis was performed in the group of patients for which GP consultation, drug dispensing and patients census data were available (n=671)
b Odds ratios adjusted for the variables shown in Table 2, that is the covariates significant in the univariate analysis at a p-value less than 0.1, including patient sex
c rc. = reference category

Discussion

Our findings demonstrate the importance of the initiation phase of antidepressant therapy, which has often been overlooked in previous research. Over one in four patients receiving a first-time antidepressant prescription from the GP decline treatment: 4.2% do not fill the prescription at the pharmacy and 23.7% fill only a single prescription. Declining the first-time antidepressant prescription is more common in patients who consult their GP for a non-specific indication, such as feeling depressed, sleeping problems, fatigue or relation problems, rather than for the specific indications depression, anxiety, panic or OCD. In addition, non-western immigrants and patients over 60 years of age were more likely to decline treatment.

The strength of our study is the availability of the population-based dataset, which combines GP consultation, drug dispensing and patient census data, and thereby providing more patient specific information. Linking GP prescribing and pharmacy dispensing data enabled us to determine the incidence of patients who do not fill their first-time antidepressant prescription. Studies on drug adherence often measure persistence, defined as the time between the first and last taken dose. These studies, however, often exclude patients who do not fill or fill only a single prescription. In view of the considerable number of patients concerned, namely over one in four patients receiving a prescription for a new treatment, the findings from previous studies need to be placed in a different perspective. Furthermore, in contrast to most regular dispensing databases, we had information

on the indications for which the patient consulted the GP, which we have shown to be very relevant.
The main weakness of the study is the lack of insight into the decision making process in the clinical encounters and into the patients' decision to decline treatment. Our study does not provide information on the reasons for not filling or filling only a single prescription, and on whether decline of treatment was intentional or unintentional. Furthermore, we do not know whether the GP was involved or informed of patients' decision to decline treatment. It is, however, unlikely that patients who do not fill their prescription at the pharmacy or fill only a single prescription discuss their decision to decline the prescription with the GP. Previous studies showed that more than half of the patients discontinuing antidepressant treatment in an early stage do not feel the need to inform their GP of stopping (7,20,24).

Patients with non-specific psychological symptoms are more likely to decline the first-time antidepressant prescription. In clinical practice, antidepressants are prescribed for a broad range of indications, including mental and psychological problems other than depression or anxiety (12,25,26). Antidepressants used for indications other than depression and anxiety have shown to be correlated with discontinuation of drug taking (12,26). Our study shows that the indication is an important factor during the initiation phase of treatment as well.
There may be several reasons for patients declining antidepressant drug therapy. First, patient and GP may not have a shared understanding of the problem and its treatment, and the patient doesn't have the prescription dispensed. There seems to be a disparity between patients' attitude towards antidepressant treatment and GPs' perceptions of their attitudes (27,28). GPs generally see the depressive symptoms against a background of patient's family history, physical illness, life events, and degree of disability (29,30). They seem to use non-specific clinical cues such as distress and impairment, as well as their knowledge of the patient, in diagnosing the illness (31). Mild depressive symptoms and psychological emotional problems can be associated with significant functional impairment, which physicians may feel inclined to address (30). Patients, on the other hand, may not all expect to receive a prescription when consulting the physician (32). Studies have shown that the majority of patients in general practice prefer treatment approaches for emotional problems that go beyond antidepressant medication (33,34). Most of them just expect the GP to listen to their problems and hope for an understanding attitude (35). Second, the patient may agree with the decision to prescribe treatment, but changes his or her mind in the light of further information or conversations with others. These patients may either not dispense the prescription or not initiate antidepressant drug taking. Finally, the patient may start taking antidepressants, but

stop them quickly. In a previous study in patients filling only a single prescription of an SSRI, we showed that fear of side effects and the actual occurrence of side effects are main reasons for not filling a second prescription (20). Antidepressant side effects may occur immediately after start, while it usually takes some weeks before patients experience recovery of symptoms (36). Side effects appear to be difficult to tolerate as they make patients feel even worse with treatment. An aversion towards medicine use and feeling better in the meantime were considerable reasons for not taking the medication for longer than two weeks (20).
Our study also showed non-western immigrants and patients aged over 60 to be more likely to decline the antidepressant prescription. In both groups, declining the prescription might be attributed to a lack of understanding about the illness and treatment. Non-western immigrants may have difficulties communicating in Dutch, but cultural factors as well may influence patients' attitude towards drug taking (37). A study in the same Dutch population found non-western immigrants to be more vulnerable for non-adherence in a later stage of treatment as well (12). Both the mentioned study and a study by Hansen et al., however, do not observe an influence of age on early discontinuation (12,18). However, the greater part of patients included in these studies used the medication for longer than 14 days, which was the maximum duration of use for the majority of patients in our study. The Dutch study further showed that women were less likely to be early dropouts. We found in the same population an effect of patient sex only in the group of nonfillers, that is women being more likely not to fill their prescription at the pharmacy. Finally, in contrast to the results from the Danish study, which reported a higher risk for early discontinuation in patients of low socio-economic status, we did not find a clear effect of sociodemographic characteristics on declining the first-time prescription.

To summarise, the present findings imply that initiation of antidepressant therapy deserves more attention in research and clinical practice. Over one in four patients who receive a first-time antidepressant prescription decline treatment. More research is needed into the implications of declining antidepressant treatment. In addition, the decision making process in clinical encounters, especially considering the perspective of the patient, requires attention. In practice, GPs could be more aware of the possibility of patients declining a first-time antidepressant prescription. They need to engage with patients' priorities and concerns, and could ask patients whether they believe an antidepressant would be helpful in treating their symptoms.

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2.2 Characteristics and reasons associated with nonacceptance of selective serotonin-reuptake inhibitor treatment

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Abstract

Introduction

Studies have shown that up to 38% of patients who start treatment with antidepressants fill only a single prescription at the pharmacy, apparently not accepting treatment. The objective of this study was to determine characteristics and reasons associated with nonacceptance of selective serotonin-reuptake inhibitor (SSRI) treatment.

Methods

A retrospective study was conducted in 37 community pharmacies in the Netherlands; patients who presented a prescription from a general practitioner (GP) for a newly started SSRI treatment were selected. Nonaccepters were defined as patients who filled only one SSRI prescription; patients who received at least three fills of an SSRI prescription were defined as accepters. Patient characteristics were obtained from automated dispensing records and from questionnaires. Areas of evaluation included sociodemographics, disease, and treatment. Nonaccepters were asked their reasons for not filling second prescriptions.

Results

Of the patients who started SSRI treatment, 22.0% were nonaccepters, filling only a single prescription. Fifty-seven nonaccepters and 128 accepters were included in our analysis. Nonacceptance was more common among patients with a low level of education (OR 2.6; 95% CI 1.1 to 5.9) and in patients who reported non-specific symptoms like fatigue, stress and restlessness as the reason for SSRI use (OR 2.7; 95% CI 1.4 to 5.5). Of the nonaccepters, 29.8% (n=17) did not start SSRI use, and 70.2% (n=40) discontinued SSRI use within two weeks. Fear of adverse effects and the actual occurrence of adverse effects were main reasons for not accepting SSRI treatment. Of the nonaccepters, 55.0% discontinued treatment without informing their GPs.

Conclusion

Acceptance of SSRI treatment is a decisive moment in a patient's adherence to treatment initiated by his or her GP and deserves more attention; GPs and pharmacists should address treatment issues, especially in groups at risk for nonacceptance.

Introduction

Guidelines recommend that treatment with antidepressants be continued for at least six months after remission of depression or anxiety-related symptoms (1,2). Since the introduction of the selective serotonin-reuptake inhibitors (SSRIs), the vast majority of patients who receive antidepressant treatment start with SSRIs, which are predominantly prescribed by general practitioners (GPs) (3). Studies show that up to 38% of patients who start treatment with antidepressants fill only a single prescription at the pharmacy (4-6). Thus, many patients have discontinued treatment long before the recommended minimum duration.

Patients who start SSRI treatment may need to overcome several hurdles. Receiving a first prescription for antidepressant medication is often considered a distressing event. During this initial consultation, patients who are depressed may experience difficulty absorbing the information given (7). Also, following initiation of SSRI treatment, adverse effects may occur before any therapeutic effect is perceived (8).

The course of drug use has been described as consisting of three parts: acceptance of the treatment plan leading to initiation, execution of the drug regimen, and eventual discontinuation (9). Studies on non-adherence seldom clearly distinguish between these phases (5,10-13). Specific studies on patients who have declined treatment are scarce; as a consequence, the acceptance phase of drug treatment has received little attention. The objective of our study was to determine whether sociodemographic, disease or treatment characteristics are associated with nonacceptance of SSRI treatment and describe the reasons that patients fill only a single prescription of an SSRI at the pharmacy.

Methods

Setting

Of a total of 1650 Dutch community pharmacies, 400 belong to the pharmacy practice research network of the Department of Pharmaceutical Sciences of Utrecht University (UPPER). These pharmacies participate regularly in research activities of the Department of Pharmaceutical Sciences and were invited to participate in this study. Forty pharmacies responded positively and provided information from their databases; three of these did not contact their patients with questionnaires. All pharmacies had automated dispensing records that provided drug utilisation information, including date dispensed, drug name, dosage, quantity, type of prescriber, and patient sex and date of birth. Since the majority of patients in the Netherlands are registered with only one community pharmacy, independent of

prescriber, pharmacy records are virtually complete with regard to prescription drugs (14).

Population

The participating pharmacies performed the selection procedure between September 2005 and July 2006. Pharmacies selected all patients aged 18-80 years who presented a prescription for an SSRI (paroxetine, fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline, low-dose venlafaxine). SSRIs must have been prescribed by a GP within the previous four months, and patients could not used any antidepressant in the year before the date of their first prescription for an SSRI. The pharmacies sent the anonymous dispensing records to the investigators, who identified potential nonaccepters and accepters. Nonaccepters were defined as patients who filled a prescription for an SSRI that was not followed by a second prescription for an antidepressant within four weeks after the theoretical end date of the first prescription. Patients were defined as accepters when the first prescription was directly followed (within one week after the theoretical end date) by two or more consecutive prescriptions of the same SSRI. In the Netherlands, it is usual practice to dispense a 14 day supply for new drug prescriptions. Subsequent prescriptions are usually for a 30 day supply. The study was approved by a medical ethics committee. All patients provided informed consent.

Characteristics and reasons for nonacceptance

Patient characteristics, including age, sex, SSRI used, and concomitant use of benzodiazepines, were extracted from the pharmacies' automated dispensing records. Other patient characteristics were obtained through questionnaires. The pharmacists contacted eligible patients, by telephone or mail, to complete a questionnaire. The questionnaire was pre-tested among a group of 25 volunteers of varying ages and levels of education and contained questions concerning the patient's employment status, living situation, level of education, reason for SSRI use, adverse effects experienced during SSRI use, additional psychotherapeutic therapy (including all types of approaches aimed at improving mental health through communication), and previous use of psychiatric drugs for similar symptoms. Education was divided into three categories: low (primary/secondary school), middle (vocational school) and high (higher professional/university). Patients could indicate whether adverse effects occurred during treatment by completing a list of the 13 most common SSRI-related adverse effects or adding adverse effects not mentioned in the list. To explore the reasons for nonacceptance, the questionnaire also asked nonaccepters whether the SSRI had actually been discontinued, the reason for discontinuation, on whose initiative the SSRI was discontinued, and whether the GP has been contacted or informed about treatment discontinuation.

Subsequently, nonaccepters were classified into two subgroups, namely nonstarters (patients who did not start SSRI use) and discontinuers (patients who started SSRI use but discontinued the treatment within two weeks.
When patients responded, their GP was contacted and asked to complete a questionnaire on their patient's reason for use of the SSRI and severity of symptoms.

Data analysis

To explore possible bias in the selection of participants, respondents and non-respondents were compared by age, sex, SSRI prescribed, and concomitant use of benzodiazepines. To determine characteristics associated with nonacceptance, the characteristics of nonaccepters and accepters were compared and expressed as an odds ratio and 95% confidence interval. Descriptive analyses were used to describe reasons for nonacceptance. We used the nonparametric Mann-Whitney U test for ordinal outcome variables not distributed normally and Chi-square test for the categorical outcome variables. Data were analysed using SPSS, version 12.0 (SPSS Inc., Chicago, IL).

Results

Selection and response

Of all patients who started SSRI treatment, 22.0% filled only a single prescription of an SSRI at the pharmacy (nonaccepters). Figure 1 shows the selection and response of the nonaccepters and the accepters, that is, the patients who filled at least three consecutive SSRI prescriptions. The questionnaire was received from 37.4% (n=61) of the nonaccepters and 51.6% (n=128) of the accepters. Four nonaccepters were excluded because they reported that they actually had not discontinued their SSRI treatment, leaving 57 nonaccepters who were included in the analysis. Two of the excluded patients indicated that they used the SSRI on an "if needed" basis.
Comparing respondents (n=189) with nonrespondents (n=222), respondents more frequently used a benzodiazepine and an SSRI concomitantly (32.3% vs 16.7%, respectively; $p<0.001$). There were no significant differences between groups with regard to age, sex, or type of SSRI prescribed.

Characteristics of nonaccepters and accepters

Table 1 shows the characteristics of both nonaccepters and accepters. Of all patients, 99 (53.5%) were prescribed paroxetine, 28 (15.1%) citalopram, 17 (9.2%) venlafaxine, 15 (8.1%) fluoxetine, 15 (8.1%) sertraline, 9 (4.9%) fluvoxamine, and 2

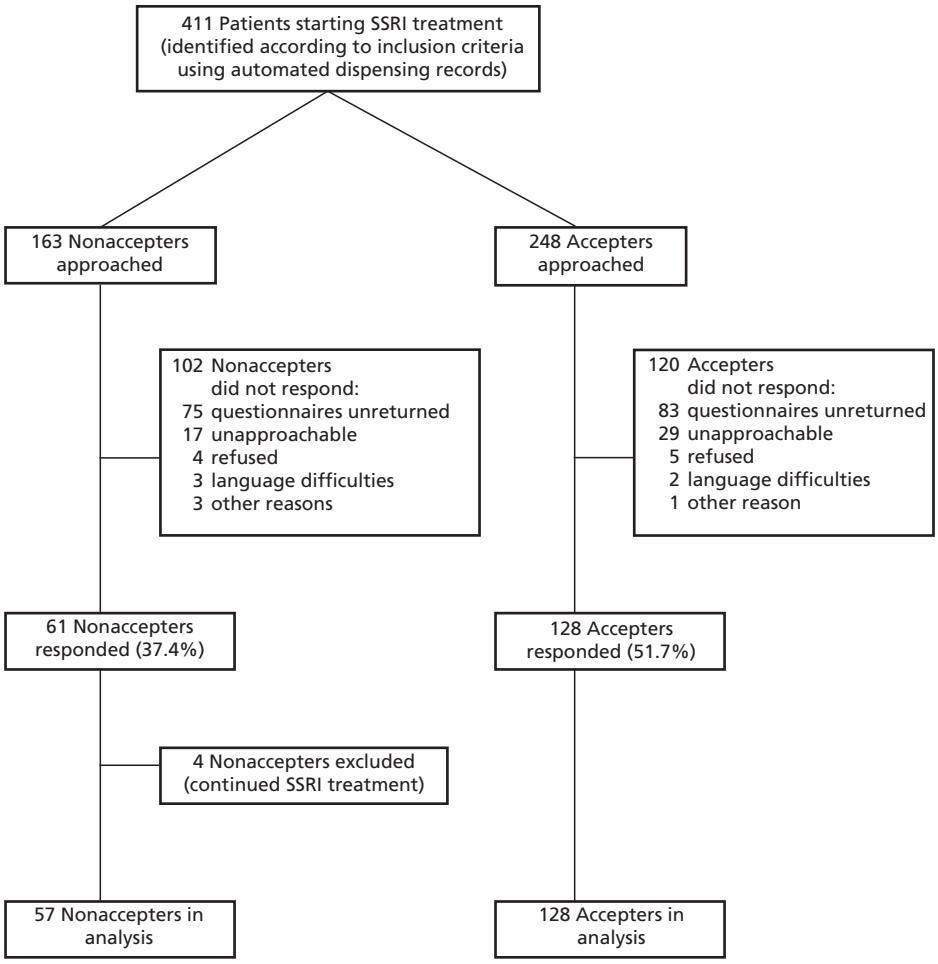

Figure 1 **Selection and response of the study participants. Patients who filled only a single prescription of an SSRI at the pharmacy were defined as nonaccepters and patients who filled at least 3 consecutive SSRI prescriptions were defined as accepters**

(1.1%) were prescribed escitalopram. There were no significant differences between nonaccepters and accepters regarding type of SSRI prescribed. Nonacceptance was significantly more common among patients with a low level of education and patients who reported non-specific symptoms such as fatigue, stress and restlessness as the reason for SSRI use. Furthermore, nonacceptance was more common among patients older than 60 years of age.

There was no significant difference in the number of patients who reported one or more adverse effects when comparing the nonaccepters who started SSRI use (discontinuers, n=40) with the accepters (70.0% vs 63.3%; $p>0.05$). However, the discontinuers reported significantly more adverse effects compared with the

Table 1 Characteristics of SSRI nonaccepters and accepters [a]

Parameter	Nonaccepters (n=57), n (%)	Accepters (n=128), n (%)	OR (95% CI)
Sociodemographic			
Sex			
female	37 (64.9)	80 (62.5)	reference
male	20 (35.1)	48 (37.5)	0.90 (0.47-1.73)
Age (years)			
18-30	7 (12.3)	22 (17.2)	reference
31-45	22 (38.6)	48 (37.5)	1.44 (0.54-3.87)
46-60	16 (28.1)	43 (33.6)	1.17 (0.42-3.26)
>60	12 (21.1)	15 (11.7)	2.51 (0.80-7.86)
Education			
high	9 (16.7)	39 (31.2)	reference
middle	10 (18.5)	27 (21.6)	1.60 (0.58-4.48)
low	35 (64.8)	59 (47.2)	2.57 (1.11-5.94)
Employment status			
employed	26 (47.3)	75 (60.0)	reference
unemployed	29 (52.7)	50 (40.0)	1.67 (0.88-3.2)
Living situation			
partner	38 (69.1)	78 (61.9)	reference
no partner	17 (30.9)	48 (38.1)	0.73 (0.37-1.43)
Disease and treatment			
Reason for use according to patient [b]			
depression	35 (62.5)	107 (83.6)	0.33 (0.16-0.67)
anxiety/panic/compulsive disorder	15 (26.3)	51 (39.8)	0.54 (0.27-1.07)
other	21 (37.5)	23 (18.0)	2.74 (1.35-5.54)
Type of SSRI			
paroxetine	28 (49.1)	71 (55.5)	reference
citalopram	13 (22.8)	15 (11.7)	2.20 (0.93-5.20)
other	16 (28.1)	42 (32.8)	1.27 (0.40-4.04)
Previous use of psychiatric medicines	15 (26.3)	41 (32.0)	0.76 (0.38-1.52)
Concomitant use of benzodiazepines	20 (35.1)	43 (33.6)	1.07 (0.55-2.06)
Psychotherapeutic therapy	22 (38.6)	66 (51.6)	0.71 (0.38-1.35)

a Numbers do not total 57 and 128 for each question, because some patients did not complete all questions.
b Patients could indicate more than one reason for use. Thus, not indicating the particular reason for use was chosen as the reference category for calculating the odds ratio.

accepters (2.9 vs 1.8; p=0.03). Dizziness, tremor, restlessness, and palpitations were reported significantly more frequently by the discontinuers.

Reasons for nonacceptance of SSRI treatment

Figure 2 shows the reasons for nonacceptance of SSRI treatment. Of all nonaccepters, 29.8% (n=17) did not start SSRI use, while 70.2% (n=40) discontinued SSRI use within two weeks of treatment; about half of the patients discontinued the SSRI within four days. The nonstarters more often received additional psychotherapy

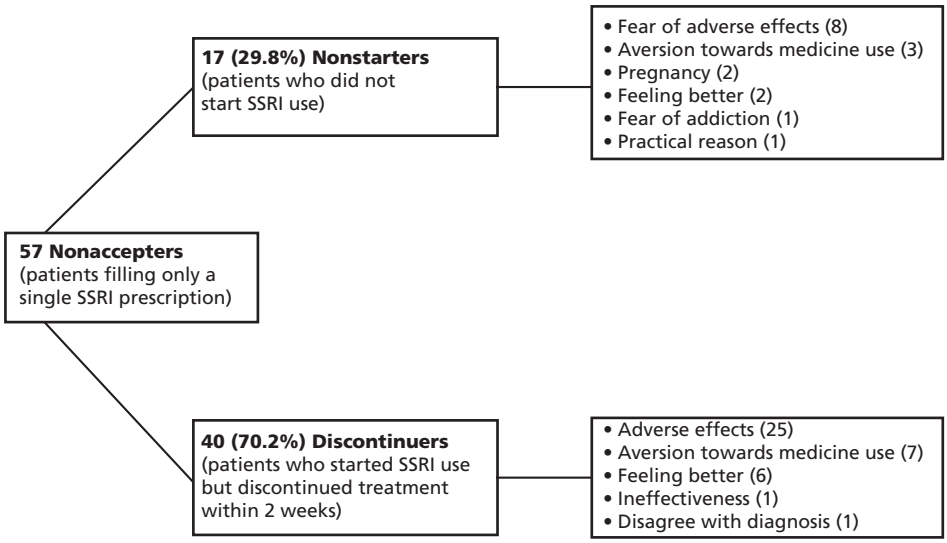

Figure 2 Reasons for nonacceptance of SSRI treatment

(58.8% vs 30.0% of the discontinuers; p=0.041) and showed a trend for less frequent use of benzodiazepines (17.6% vs 42.5% of the discontinuers; p=0.072). The other characteristics did not differ. The discontinuers who stopped taking the SSRI due to adverse effects experienced a mean number of 4.3 adverse effects. All discontinuers who indicated anxiety or panic as the reason for SSRI use (n=10) discontinued treatment because of adverse effects versus 59.1% of the discontinuers indicating depression as the reason for use (n=22). Of the discontinuers, 55.0% (n=22) discontinued the SSRI on their own initiative and did not inform the GP about stopping, 40.0% (n=16) discontinued the SSRI on their own initiative but after consulting the GP, and 5% (n=2) discontinued the SSRI on advice of the GP.

Patient versus GP perceptions

GP questionnaires were received for 53.0% (98) of the responding patients. According to the GP responses, there was no significant difference in reason for use and severity of symptoms between the nonaccepters and accepters. Depression was indicated for 60.7% (n=17) of the nonaccepters and 65.7% (n=46) of the accepters, while anxiety, panic, or obsessive-compulsive disorder (OCD) was indicated for 35.7% (n=10) of the nonaccepters and 30.0% (n=21) of the accepters. For 21.4% (n=6) of the nonaccepters and 32.9% (n=23) of the accepters, the severity of symptoms was considered to be severe.

However, there was a significant difference between nonaccepters and accepters when comparing the reason for use as reported by patient and GP. When GPs made a diagnosis of depression, 35.3% (n=6) of the nonaccepters and 4.3% (n=2)

of the accepters (p=0.001) reported non-specific symptoms like fatigue and stress. When GPs diagnosed anxiety, panic, or OCD, 30.0% (n=3) of the nonaccepters and 14.3% (n=3) of the accepters reported non-specific symptoms as the reason for use of the SSRI (p>0.05).
In addition, there was a significant relationship between the severity of symptoms according to the GP and the reason for use according to the patient. When GPs considered the symptoms to be mild or moderate, 28.6% (n=6) of the nonaccepters and 4.3% (n=2) of the accepters (p=0.005) reported non-specific symptoms as the reason for use.

Discussion

Our study indicates that fear of adverse effects and the actual occurrence of adverse effects are the main reasons for not accepting SSRI treatment. In addition, a considerable number of nonaccepters indicated that they felt an aversion towards medicine use, were feeling better in the meantime, or disagreed with the GP's diagnosis. One in three nonaccepters actually did not start SSRI therapy, while the other nonaccepters discontinued SSRI use within two weeks. More than half of these patients discontinued treatment on their own initiative without informing the GP. Nonacceptance was more common in patients with a low level of education and in those who reported non-specific symptoms like fatigue, stress and restlessness as the reason for SSRI use. In addition, there was a trend for nonaccepters to be over 60 years of age.

SSRIs can cause annoying adverse effects, such as gastrointestinal problems, palpitations, dizziness, and restlessness, which may occur within several hours, while it may take several weeks before any therapeutic effect is perceived. Being aware of this phenomenon may be crucial for patients to tolerate the first weeks of treatment. Fear of adverse effects, which prevents patients from starting antidepressant therapy, may be caused by the information received with the prescription. Some patients indicated in the questionnaire that reading about adverse effects in the patient information leaflet made them anxious about starting SSRI use. This does not mean that information on adverse effects should not be disclosed to the patient. On the contrary, discussing adverse effects in advance and during treatment encourages the initiation and continuation of antidepressant therapy (15). Patients who retained certain educational messages during their initial physician visit were more likely to continue their antidepressant during the first month of therapy (16). It may be possible that adverse effects were not discussed with the nonaccepters in our study.

There appears to be a difference in the perception of the illness between patients and their GP. This difference was also seen in the reason for use as reported by patient and GP. Unlike their GPs, the nonaccepters more often labelled their symptoms as stress or fatigue. This difference in perception with respect to the underlying problem is especially striking for depression. One in three nonaccepters whose GP made the diagnosis of depression did not feel that they were depressed. It is clear that patients consider their problem to be less serious than the level of severity according to the GPs. This is an important finding, because adherence is less likely when patients have the perception that they do not need psychiatric care or that their problems are minor (17). Moreover, not all patients expect to receive a prescription when consulting the physician (18). In general, patients consider psychiatric drugs to be hazardous and do not want to take them when they are not considered necessary (19,20). About half of the patients expressed concerns about the long-term effects of taking antidepressants, which is associated with medication-taking behavior (21). Therefore, physicians should ask their patients how they interpret their symptoms and whether they believe prescribing an SSRI would be helpful in treating these symptoms. Medication beliefs and attitudes seem to be important predictive factors for the appropriate use of antidepressants and should be considered (11).

A lower education level and age over 60 years were associated with nonacceptance of antidepressant treatment. Other studies on education as a determinant of discontinuation also suggest some influence, especially in the early phase of treatment (10,22). Many elders resist the use of antidepressants, while a communication gap between the elderly and physicians has also been shown to exist (23,24). Health professionals should make an effort to ensure that less educated and elderly patients understand the key educational messages for SSRI use.

This study provides insights into the process of acceptance of SSRI treatment initiated by GPs. The strength of our study is that we received data directly from patients and their GPs. Patients' perspectives on treatment are essential in understanding health-related behaviour. Moreover, patients may provide information on which GPs and other healthcare providers are not always aware. Patients may be reluctant to communicate negative treatment experiences to their GP, since many patients do not inform their GP when they stop taking their prescribed drugs (4,13).
Our findings must be seen in light of several limitations. First, the selection of patients may have introduced bias. The responders used concomitant benzodiazepines more often than non-responders used this drug class; we do not have a plausible explanation for this. We hypothesised that patients who accepted their SSRI treatment might be those with a longer history of symptoms and more

concomitant benzodiazepine use. However, there was no difference between the accepters and nonaccepters regarding benzodiazepine use.
In addition, memory failure and socially desirable responses may have contributed to the difference between patient and GP perceptions regarding the reason for medication use. Patients may judge their clinical situation differently several weeks after receiving the prescription or after visiting the GP to justify their decision to not to start or to discontinue the treatment.
Finally, the response rate and power of the study should be examined. The response rate, especially of the nonaccepters, was rather low. During contacts between the participating pharmacists and patients who had not yet started or who had used the antidepressant for only a couple of days, it appeared that patients often could not be convinced that their views on antidepressant use were relevant for research. Therefore, our picture of the nonaccepters may not be representative of all patients who fill just a single prescription at the pharmacy. Moreover, the reasons for responding or not responding may be different between the accepters and nonaccepters. The power of our study may be considered relatively low; however, this study is the first to survey a group of patients who do not accept a treatment that their physician thought appropriate. Future studies in larger groups may widen the knowledge and understanding of this relevant issue.

In conclusion, patient acceptance of SSRI treatment is a decisive moment in adherence to treatment initiated by GPs and deserves more attention. GPs and pharmacists should be cognisant of patients' attitude and beliefs towards SSRI use, and GPs should ask patients how they interpret their symptoms and whether they believe an SSRI would be helpful in treating these symptoms. Prescribing an SSRI as a shared decision between physician and patient in a trusting relationship may deter patients from discontinuing treatment without informing their physician. GPs and pharmacists should address treatment issues especially in patients who are at risk for nonacceptance, such as the elderly and those who are not well educated.

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2.3 Patients' perceptions of information received at the start of selective serotonin-reuptake inhibitor treatment: implications for the community pharmacy

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Abstract

Introduction

Although pharmacists intend to provide adequate information to patients, it is unclear how this is implemented in practice and whether it fulfils patients' needs. We examined patients' perceptions of information they received on selective serotonin-reuptake inhibitors (SSRI) at the start of treatment, aiming to identify (1) information needs and (2) the potential role of the community pharmacy as information provider.

Methods

A qualitative descriptive study which comprised semi-structured telephone interviews, carried out in patients who recently started a new course of SSRI treatment. Patients were recruited through ten community pharmacies in the Netherlands. The interviews were guided by a list of topics, including type of information obtained, unmet information needs, relevance of information issue, provider of information, and role of the pharmacist.

Results

Forty-one patients took part in the interview. Patients starting treatment with antidepressants feel they would benefit from information tailored to their personal needs and preferences for involvement. Many patients require more concrete and practical information on adverse effects and the delayed onset of action. In addition, explaining the term dependency in the context of SSRI use, discussing the necessity for use and the believed harms of long-term treatment is important for patients. However, information needs and the desired level of involvement vary largely between patients. The role of the pharmacy in the provision of information is perceived as rather limited by most patients. Barriers to an improved communication are: timing of information (mainly restricted to the first dispensing), lack of time and privacy, lack of empathic involvement and a protocolised way of information provision, and inexperienced pharmacy staff.

Conclusion

Current drug information practice in Dutch pharmacies fails to meet patients' requirements. Developing and implementing a patient-centred way of information provision by pharmacies to patients beginning antidepressant treatment, needs thorough consideration. Community pharmacists need to recognise the differences in information needs between patients, and should tailor their comunication style according to patients' preferences.

Introduction

Patients often feel that they do not receive adequate information about their antidepressant treatment. During treatment many patients have questions and concerns about use of their medication (1). They feel that they would benefit from additional information about their antidepressant medication (2-4). Physicians often provide limited information when prescribing antidepressants, while omitting critical information about the anticipated duration of treatment and expected delay in onset of action (5). Further, written patient information has been criticised for being too medico-centred (3,6). The content often centres on topics of importance to professionals, but may not reflect patients' actual needs (7). From the medical point of view, providing information about antidepressant use has been considered crucial in order to increase adherence to treatment (6,8,9). As part of the development of involving patients more actively in decision making about medication, information is increasingly viewed as requisite for patients to make informed decisions (6,8,9). It is therefore important to consider patients' views on the information received at the start of antidepressant treatment. Insight in patients' perspectives may provide the knowledge to support informed decision making on initiating antidepressant treatment.

Pharmacists nowadays more and more acknowledge their responsibility in providing information and counselling to patients. Pharmacists can interact with patients during and after they dispense prescriptions. It is, however, unclear whether the pharmacists' new task is implemented in daily practice and whether patients are aware that they can ask pharmacists for drug information (10). There is some evidence that community pharmacists offer advice to patients presenting a first prescription for an antidepressant. For follow-up prescriptions, the pharmacist is often less involved (11-13). The implementation of patient education is a rather new task for community pharmacists in the Netherlands as well. Providing instructions when the drug is dispensed for the first time is regarded as a primary activity by the profession (14). Most of the dispensing work is done by the pharmacist assistants, under supervision of the pharmacist. All Dutch community pharmacies and general practitioners participate in pharmacotherapeutic consultation groups (FTOs), in which pharmacotherapy is discussed, and sometimes certain therapeutic and counselling agreements are made. Although Dutch pharmacists intend to provide adequate information to patients, it is unclear how this is implemented in practice and whether it fulfils patients' needs. Previous studies did not focus on exploring information needs of patients starting antidepressant treatment in relation to the pharmacy. To obtain a broad view of patients' needs a qualitative research method was chosen. We examined patients' perceptions of information they received on selective serotonin-reuptake inhibitors (SSRI) at start of treatment, aiming

to identify (1) information needs and (2) the potential role of the community pharmacy as information provider.

Methods

Setting and patients

This was a qualitative descriptive study which comprised semi-structured telephone interviews, carried out in patients who recently started a new course of SSRI treatment. Patients were recruited through ten community pharmacies in the Netherlands. Each pharmacy selected the patients that presented a first prescription of an SSRI in the six months before the selection date. In the Netherlands it is usual practice to dispense a 14 day supply for new prescriptions, and subsequent prescriptions are usually for 30 days supply. Potential patients were identified using the computerised pharmacy information and administration systems. Patients were contacted if they were over 18 years of age and started a new course of SSRI medication in the previous six months. Patients were excluded if they had used any antidepressant in the year before the start of the current SSRI treatment, and concomitantly used antipsychotic medication or lithium, the latter in order to exclude severe forms of depression like psychotic depression. A letter of invitation to participate, including information on the study itself, was sent to all eligible patients by the pharmacists. Patients were asked to contact the pharmacy within two weeks if they did not want to participate. The researchers subsequently tried to contact the other eligible patients directly. Ethics committee approval was not required in the Netherlands for this type of study as people were not subjected to procedures or required to follow rules of behaviour. Patients were given two opportunities to consider the request to participate and to refuse participation in the study, that is after having received the information letter and before the start of the interview itself.

Interview

All telephone interviews were completed by two researchers (MS and EvG). The interviews were guided by a list of topics identified from previous studies (2,7,15-17). Topics included type of information obtained, unmet information needs, relevance of information issue, provider of information, and role of the pharmacist. We intended to discuss in-depth respondents' experiences with the pharmacy and their views on pharmacy's potential role, but this did not stand out as clearly as expected. Respondents were also asked whether they still continued the use of the SSRI, and to indicate their level of education and employment status. The

interviews were piloted with volunteers to ensure face and content validity. The length of the interviews was between 20 and 50 minutes.

Analysis

During the interviews notes were taken, and these were worked out immediately after each interview. The constant comparative method, in which original themes are revised after comparison with newer themes generated during the coding process, was used for analysis (18). The interviews were reviewed by three of the authors. Interview transcripts were read for emergent themes and then discussed. During this process an index structure of categories was gradually developed. The transcripts were coded according to the emergent themes and categories. Throughout the process of analysis, the categories were focused and altered, until the authors agreed upon the final categories.

Results

Characteristics of respondents

One hundred and twelve patients were sent a letter of invitation to participate in the study by their pharmacist. Of these, 17 informed the pharmacist that they did not appreciate any further contact. The researchers tried to contact the other 95 patients by phone, but did not succeed in contacting 43 patients in spite of several attempts. After contacting the remaining patients, 11 of them were not able or refused to participate, while 41 patients took part in the interview after giving verbal informed consent. The characteristics of the respondents are shown in Table 1. The mean duration of SSRI use was 12 weeks. No significant differences between the respondents and non-respondents were found with respect to age, patient sex or dispensed type of SSRI.

Information needs

Respondents were asked which information they have received about their SSRI medication, and which information they would like to have had. One third of the respondents did not express a need for further information, although half of them actually obtained little information. Yet, the other two third felt they required much more information. Seven of them desired information on a specific issue, often based on a specific treatment concern or a personal experience with SSRI taking. The others felt they required much more detailed information on several topics, in order to take an informed decision about initiating treatment. In this context, some lacked information particularly on the disadvantages of SSRI use. Many patients expressed a need to receive more detailed, concrete and practical advice related to

Table 1 Characteristics of the responders

Characteristic	% (n)
Age	
18-30	12.2 (5)
31-45	29.3 (12)
46-60	34.1 (14)
>60	24.4 (10)
Patient sex	
female	61.0 (25)
Level of education	
low	26.8 (11)
middle	31.7 (13)
high	41.5 (17)
Employment status	
employed	58.5 (24)
Reason for use	
depression / depressive symptoms	61.0 (25)
anxiety / panic / OCD	17.1 (7)
non-specific symptoms related to depression	14.6 (6)
other reasons	7.3 (3)
SSRI dispensed	
paroxetine	39.0 (16)
citalopram	19.5 (8)
sertraline	12.2 (5)
escitalopram	9.8 (4)
other	19.5 (8)
Treatment status	
continuing SSRI use	85.4 (35)
discontinued SSRI use	9.8 (4)
not started SSRI use	4.9 (2)

daily life medicine use. The unmet information needs are discussed below. Table 2 provides an overview of the issues in order of importance, based on perceived relevance to respondents and reported frequency.

Delayed onset of action

Most of the respondents were informed that it can take some time before the therapeutic effect is perceived, and that they even may feel worse in the beginning. Some of the respondents considered this information of vital importance. They felt rather worse during the first weeks, and believed they otherwise would have stopped taking the SSRI. Some respondents reported not being told how many weeks it usually takes to perceive an effect. Others passed the indicated initial treatment weeks and did not perceive any therapeutic benefit. Being unaware of the process of recovery and not knowing what to do in case they do not respond,

Table 2 What patients want to know about antidepressants at the start of treatment from physician and/or pharmacy staff

Information issues	Rating of importance [a]	Lack of information	Who can provide information: physician or pharmacy staff? [b]
Delayed onset of action	++	Concrete and practical info on: timing uncertainties, what if patient fails to benefit from treatment	Physician and/or pharmacy staff
Adverse effects	++	Concrete and practical info on: adverse effects relevant to patient, timing and frequency, impact, how to avoid or reduce, attribution to illness or drug, discussing concerns and experiences	Physician and/or pharmacy staff
Dependency	++	Physical dependency; Psychological dependency	Physician and/or pharmacy staff
Reason for use	+	Argue the need for use of the antidepressant and choice of SSRI specifically; Treatment alternatives; Expected benefits of medication; Biomedical explanation of illness and how antidepressants work	Physician
Consequences of long-term use	+	Suspected harms (brain damage, personality changes)	Physician and/or pharmacy staff
Interactions	+	Concrete and practical info on drug taking in everyday life	Pharmacy staff
Duration of treatment and discontinuation	+/-	Moment of discontinuation; How to taper treatment	Physician and/or pharmacy staff

a Rating of importance is based on perceived relevance to respondents and reported frequency of specific issue (++ rather relevant to most respondents, or extremely relevant to more than half of respondents; + rather relevant to half of respondents or extremely relevant to some respondents; +/- not relevant to most respondents)
b Information at the pharmacy can be provided by the pharmacist or experienced pharmacy staff

makes them feel uncertain. Respondents like to have more concrete and practical information.

Adverse effects

About half of the respondents reported to be informed on the possible occurrence of adverse effects. Others read about adverse effects in the information leaflet. Thus, many of them were aware that adverse effects could occur directly after initiation of treatment, and usually subside over several weeks. Yet, several respondents lacked information on adverse effects, including information on how to manage adverse effects or whether and when the different type of effects subside. Some respondents were informed of the possible occurrence of adverse effects, but did not expect the effects to affect them or to be that bothersome. In addition, the respondents sometimes felt uncertain about the negative effects on their daily life functioning after start of treatment, and did not know whether to attribute these symptoms to the medication or to the illness. Although adverse effects appeared to be an important topic for most respondents, a few did not appreciate any detailed

information on this. They felt that information may deter them from using the medicine, or make them extremely conscious of the possible occurrence of adverse effects. For this reason, some respondents were advised by their physician not to read the information leaflet.

Antidepressant dependency

Many respondents expressed a fear of dependency and a need for further information on this issue. The topic was often brought up on the respondents' initiative during the initial contact with the physician. Respondents seemed to refer to both physical and psychological dependency. Some regard the need for tapering the SSRI and the occurrence of withdrawal symptoms as evidence for dependence. A few had previous problems with discontinuation of benzodiazepines, and regard SSRIs as the same type of addictive drug. Other respondents were concerned about relying too much on the SSRI, instead of dealing with the cause of their problems. For some respondents the fear of dependency was a reason to discontinue treatment, to reduce the dosage or use the SSRI intermittently.

Reason and explanation for use

Respondents differed largely in their need to know why they were prescribed an SSRI and how it works. Most of them were informed on the reason for use and which effect they might expect. For some respondents this information was sufficient. Others needed much more information to feel confident that start taking SSRIs is a good decision. The biochemical model to explain depression and how antidepressants work, the motivation for prescribing an antidepressant and the SSRI specifically, together with alternatives of medicine treatment, were issues that needed more attention. A few respondents were disappointed not to be informed about the reason for using an SSRI and the fact that it was an antidepressant they had received.

Harmful consequences of long-term use

Some respondents felt that they lacked information on the disadvantages of SSRI use. Particularly information on the supposed harms of long-term SSRI use, like brain damage and personality changes, was required. Respondents often were actively seeking for further information on these issues from other sources. It seems advantageous for healthcare professionals to discuss these concerns during initiation of treatment, so that respondents may feel more confident with treatment.

Duration and discontinuation of treatment

Half of the respondents reported that duration of treatment was not discussed at the start of treatment. Some of them did not feel a need to be informed on the recommended treatment time, as it was not considered to be an issue at the start of treatment. The other half of the respondents were told that the SSRI had to be taken for a longer period of time, at least for half a year and in some cases through life. Less than half of the respondents were aware that the SSRI should be

tapered when discontinuing treatment. The other respondents did not give much thought on this issue and believed it might be brought up when the moment of discontinuation had come.

Role of the pharmacy as provider of information

Respondents were asked from whom they received the information on the antidepressant and how they viewed the information received by the pharmacy. In addition, respondents were asked to give their view on the potential role of the pharmacy as provider of the required information at the start of treatment.

Current practice

The respondents had received most information from their prescribing physician. Most of the respondents felt the physician is the most appropriate person to inform them about SSRI treatment. They often have a trusting relationship with their physician, who is acquainted with their personal circumstances. They felt it is the physician's responsibility to argue the choice for the SSRI, as he/she prescribes the medicine. The information received from the pharmacy was regarded as rather limited, and sometimes perceived as standard talk. Information was often restricted to an explanation of the drug label, a referral to the information leaflet, or the message that the pharmacy could be contacted in case of any questions. Some also reported a positive experience they had with the pharmacy, like the signalling of an interaction with concomitant medication or solving a practical problem with splitting of capsules. Next to the package insert, many respondents received a personalised information leaflet, including the patient name. Except the few respondents who reported not having read the information, most appreciated the written information. It was helpful to return to when they had questions or felt uncertain about certain effects experienced with treatment. However, several reported that the information was difficult to interpret, raised new questions, or was too general and not sufficient specific for their situation. Some required more information, and searched for information on the internet.

Some respondents commented to see the pharmacy only as a take away centre. Others did not consider the circumstances at the pharmacy to be favourable in order to receive the required information. Several objections were raised to an extended role of the pharmacy in the provision of information. Respondents sometimes felt reticent to raise questions and concerns. They had the impression that pharmacy assistants felt uncomfortable with their role as provider of information on antidepressants. Others missed an empathetic and personal involvement from pharmacy staff. Also, a lack of privacy at the pharmacy, limited time for personal contact, concerns about receiving confusing or contradictory information from different sources, and the quality of verbal information by pharmacy staff were considered to be important barriers.

Box 1 Meeting patients' information needs at the start of antidepressant treatment: suggestions for the pharmacy

- Information on antidepressants should be provided by the pharmacist or experienced pharmacy staff.
- Good communication skills are required for an optimal individualised interaction with patients.
- Information should be personal rather than protocolised. Not every patient wants to be equally informed.
- Inquire about each patient's individual needs for information. Discuss patient's treatment concerns.
- Inquire about patient's preferred ways to receive the required information.
- Information should be concrete and practical, instead of vague and general.
- Concentrate on information related to the medicine rather than patient's symptoms and reason for use.
- Explain the information leaflet, focus on issues of importance to the patient. If required, provide the patient with other sources of information, such as reliable websites.
- Check whether any information was contradictory or confusing.
- Information must not be restricted to the initial visit. Follow-up consultations, either at the pharmacy or by telephone, are desired.
- Discuss patients' experiences with antidepressant use during follow-up contacts.
- Be aware of privacy circumstances and patient anxieties about time.

Suggestions for improved practice

In first instance, it seemed to be difficult for some respondents to come up spontaneously with clear thoughts on the role for the pharmacy as information provider. Nevertheless, analysis of the interviews revealed several clues and suggestions to extend the role of the pharmacy for the benefit of patients. Box 1 provides an overview of these suggestions. Patients required more concrete and practical information on SSRI treatment, including the onset of action, preventing and reducing of adverse effects, interactions and fear of addiction. Next to these issues, other practical issues that influence patients' daily lives like driving, alcohol use, missing doses and splitting of tablets, could be addressed by pharmacies. One patient for example preferred to discuss the occurrence of light flashes, an adverse effect, with his pharmacist instead of the physician. Some also commented not seeing a role for the pharmacy in discussing the need for treatment, as pharmacists are not acquainted with patient's illness and personal circumstances. In this respect, it is essential that pharmacies concentrate on information related to the medicine itself rather than to the symptoms and situation of the patient. Respondents feel that pharmacy staff should try to assess patient's information needs and preferences for involvement. A more empathetic and personal involvement from pharmacy staff is sometimes seen as a requisite for a more pronounced role as provider of information.

Some respondents suggested pharmacy staff to explain the information leaflet during the initial visit. Others would like to have received suggestions for websites offering reliable information. Some felt e-mail contact with the pharmacist

to be valuable, others however perceived this as impersonal and evoking new questions. Several respondents would appreciate pharmacists to arrange follow-up consultations with the pharmacist or experienced pharmacy staff. There is a large amount of information required at the start of treatment, which cannot be provided in a single contact. Some respondents reported that they had difficulty to absorb all the information received at the initial visit. They believe it would be advantageous to discuss their personal experiences with SSRI use, and raise questions and concerns that came up during use or when reading the information leaflet. The follow-up consultations, could be held either when patients return to the pharmacy for a second dispense of the SSRI, or by telephone after one or two weeks of treatment. The latter was preferred by some of the respondents who did appreciate to discuss their experiences and concerns with the researchers during the interview.

Discussion

The findings from this study indicate that the current information patients receive at the start of SSRI treatment does not meet their needs. Patients starting treatment with antidepressants would benefit from information tailored to their personal needs and preferences for involvement. Many patients require more concrete and practical information on adverse effects and the delayed onset of action. Discussing the potential consequences for everyday life functioning beforehand, would patients feel more prepared and supported during use. In addition, explaining the term dependency in the context of SSRI use, discussing the necessity for use and the believed harms of long-term treatment is important for patients. However, information needs and the desired level of involvement vary largely between patients and depend on different factors, including patients' previous experience with antidepressants, attitude toward use, specific concerns about use and information already received. The role of the pharmacy in the provision of information is perceived as rather limited by most patients.

Limitations of the study can be found in the nature of the illness and the selection of respondents. Our respondents sometimes had difficulty responding on more in-depth questions, which may be due to their current state of illness during the initial phase of treatment. Another explanation may be the unfamiliarity with the pharmacy as provider of information. Further, most of the respondents were still continuing SSRI taking, which is more than we expected according to the discontinuation rates assessed in observational studies (15,19,20). It might well be that patients discontinuing treatment early have other views and needs than the

patients surveyed in our study. Yet, the respondents had a range of sociodemographic characteristics and no difference was found between respondents and non-respondents regarding age, patient sex or type of SSRI prescribed.

The information needs of our patients are complementary to the needs revealed in other studies (2,7). Information regarding dosage prescribed related to minimum and maximum dosages was not brought up by our patients. In addition, our patients gave less mention of information needs relating to duration and discontinuation of treatment. Many of them considered this to be less relevant, as they recently started treatment. On the other hand, many of our patients felt that they needed more information to feel confident that starting antidepressant use was inevitable. In this context the biochemical model of depression as an illness mediated by decreased concentrations of neurotransmitters, and antidepressants increasing the neurotransmitter concentrations back to normal, is sometimes found to be helpful. This biochemical explanation helps to remove concerns about personal weakness, but must be used cautiously (7). Patients use and interpret the model in different ways, and it may reinforce patient's dependency on medicines rather than seeing antidepressants as part of the solution (7). Furthermore, it is obvious that patients' experiences with antidepressant treatment raised concerns and uncertainties that were not covered in the verbal or written information received at the start. Patients beginning antidepressant treatment require further information to consider benefits and risks (3).

Our findings demonstrate a discrepancy between intentions and practice. Dutch pharmacists regard the provision of information as a primary task and put much effort in the implementation of information instructions for patients who present with a first prescription. In addition, pharmacists expressed a positive attitude towards a wider role in the care of depressive patients (12). Patients, however, do not perceive the contribution of the pharmacy as significant and do not consider the provision of information to be the responsibility of the community pharmacy. They seem to be unfamiliar with the pharmacist's task as information provider (10,21). This may not be surprising as reported activities of community pharmacists showed that pharmacists are doing little as intermediaries between patients and physicians (12,16).

There are several explanations for the limited role patients attribute to the pharmacy. In the Netherlands the dispensing work is usually done by pharmacist assistants. Although all pharmacist assistants completed a 3-year training and certification, the provision of adequate information on drug taking tailored to each patient's individual needs is a complex task, requiring specific pharmacotherapeutic knowledge, communication skills and experience. The nature of the disease also

complicates the communication process. Pharmacy staff may not feel confident to communicate with patients having an emotional disorder, and therefore feel reticent to provide information on antidepressants. Patients themselves experience lack of time and privacy as barriers to an improved communication in the pharmacy. In addition, patients report to have difficulty recalling the information received at start of treatment (2). Pharmacies restrict the provision of information mainly to the first-time prescription contact, in which a large amount of information has to be given. Finally, patients seem to receive information at the pharmacy which does not match their personal needs, in a way they do not regard as appropriate. The understanding of pharmacists about what information patients should be provided with has been found to differ from the patients' understanding (22). Patients consider information about the use and adverse effects of their medication to be more important than pharmacists (22). Also, the patients in our study consider the information provision at the pharmacy as impersonal and protocolised. They rather prefer information tailored to their needs, and require a more empathic attitude from pharmacy staff.

Developing and implementing a patient-centred way of information provision by pharmacies for patients beginning antidepressant treatment, needs thorough consideration. First, healthcare professionals, particularly pharmacists and physicians, should consider which type of information should be provided by whom for the benefit of patients. Physicians showed to be critical towards community pharmacists providing patients with information about the purpose of the medication (23). Most patients in our study also consider this issue to be part of the patient-physician relationship, and feel uncomfortable discussing their illness with pharmacy staff. Yet information related to the antidepressant itself can be provided by the pharmacy in any case. Second, some patients worried about getting confusing or contradictory messages when receiving information from more sources. This concern can be overcome as long as patients' uncertainties and concerns are elicited at the pharmacy, and pharmacy staff address these. Moreover, Sleath et al. showed patients receiving information from more sources to be more adherent to antidepressant treatment, suggesting that they understood their medication better (24). Anyhow, patients nowadays have access to different sources of information, like the Internet, television, magazines or friends and family members. Stopping this development is not desirable and realistic. In this context the patient information leaflet is a crucial element in the information provision process. Pharmacy staff can use the information leaflet as a guide for discussions with patients, while eliciting their concerns and uncertainties. The advantage of a leaflet is that the patient is able to return to information afterwards. However, patient information leaflets present information about medicines often with great certainty, simplicity and optimism

(3,6,8). Leaflets usually do not consider patients' concerns and uncertainties, and understate the problems patients experience in taking antidepressants (4,7). Third, timing of information is important. Pharmacists should consider repeated opportunities for information provision during the initial stage of treatment, and not limit their role to the first prescription of a new treatment. Patients' preferences for involvement vary at different points in treatment, dependent on changes in the illness state and experiences with medication (2). Follow-up contacts, either at the pharmacy or by telephone, can be used to engage with patients' experiences with antidepressant use and the concerns to which they actually gave rise. Education and monitoring by phone has shown to improve the level of patient feedback to pharmacists, and such feedback may help pharmacists identify and address their patients' misconceptions, concerns and progress with antidepressant treatment (25). Fourth, pharmacists or experienced pharmacy staff, rather than inexperienced pharmacy assistants, should take the responsibility to support patients during the initiation of treatment. Missed opportunities for providing tailored information decrease the trust patients have in the pharmacy. Finally, patients vary in their preferences for a two-way communication with healthcare professionals and involvement in treatment decision making. A simple pre-consultation checklist can be used asking patients to expand their concerns and list the issues which need to be discussed.

In conclusion, patients initiating antidepressant treatment feel they would benefit from information tailored to their personal needs and preferences for involvement. They require more concrete and practical information on adverse effects and the delayed onset of action. In addition, explaining the term dependency in the context of SSRI use, discussing the necessity for use and the believed harms of long-term treatment is important for patients. Current drug information practice in Dutch pharmacies fails to meet patients' requirements. Community pharmacists need to recognise the differences in information needs between patients, and should tailor their communication style according to patients' preferences.

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2.4 Patients' views on pharmacy-provided information on antidepressants: a survey six months after start of treatment

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Submitted for publication

Abstract

Introduction

Pharmacists have a potentially important role in providing information and advice on antidepressants. The aim of this study was (1) to describe how patients experience information on antidepressants given by the pharmacy at first prescription, and (2) to investigate whether verbal information additional to written information given at the pharmacy affects the duration of antidepressant use.

Methods

A questionnaire study in fifteen community pharmacies in the Netherlands. Patients received a questionnaire six months after starting antidepressant treatment. One hundred and five patients, aged between 18 and 80 years, who started treatment with a second-generation antidepressant, were included. Primary outcome measures were patients' views on the quality of information at the pharmacy and their views on the role of the pharmacy in patient education and counselling. Secondary outcome measures were the duration of use and the number of antidepressant prescriptions during the study period of 180 days.

Results

Patients consider the quality of information given at the pharmacy at first prescription of an antidepressant to be quite positive. However, they do not see an important role for the pharmacy in antidepressant education and counselling. Only one quarter of patients stated that they received verbal information at first prescription at the pharmacy. Patients receiving verbal information along with written information did not use their antidepressant medication any longer than patients receiving written information only.

Conclusion

There is a gap between the positive views on the quality of information and patients' need for information and discussing experiences on the one hand, and the limited role patients attribute to the pharmacy on the other. Pharmacists should be more supportive in informing and counselling patients on antidepressant treatment.

Introduction

Healthcare providers seem to play an important role in increasing adherence to antidepressants by educating patients about treatment. Studies have shown that patients who received specific information from their physician were more knowledgeable, had more positive beliefs about their medication and were more likely to adhere to antidepressant treatment (1-3). However, current practice does not seem to be optimal. During treatment many patients still have questions and concerns about the use of their antidepressant medication (4). Patients feel that they would benefit from being given more information about their medication (5). In addition, physicians appear to provide only limited information while prescribing antidepressants, often omitting critical information that may promote adherence (6).

In this study we focus on the pharmacist, who has a potentially important role in providing information and advice on antidepressants. Community pharmacists can interact with patients as they dispense prescriptions. There is some evidence that pharmacists offer advice to patients presenting with a first prescription for an antidepressant (7,8). After the use has started, pharmacists appear to have less involvement (7-9). In general, patients seem to be satisfied with their community pharmacy's services (10). Pharmacists themselves perceive several barriers to a greater involvement in giving advice on antidepressants (7). They believe that patients are not interested in engaging in discussions about the treatment of depression and feel uncomfortable discussing antidepressants because of the nature of the associated illness.

The implementation of patient education is a rather new task for community pharmacists in the Netherlands. Patient education mainly consists of providing information at the first prescription visit at the pharmacy. Drug monitoring and counselling after the initial prescription is just beginning to be developed. At the time of the study there was no legal obligation for pharmacies to provide verbal information. Yet the Royal Dutch Organization for the Advancement of Pharmacy (KNMP) has introduced the Dutch Pharmacy Norms (NAN) in 1996 (11). Although the norms were accepted by the profession, they are rather abstract and not adjusted to individual pharmacies and patients.

For a better understanding of the potential role of pharmacies in supporting patients starting antidepressant treatment, insight in patients' views on pharmacy-provided information and information needs is required. The objective of this study was to describe how patients who are prescribed a second-generation antidepressant (1) experience the information given by the pharmacy at first prescription, (2) assess their knowledge regarding antidepressant use, and (3) view the role of the pharmacy in providing information. In addition, the study aimed to assess whether

providing verbal information additional to written information along with the first prescription affects the duration of antidepressant use.

Methods

Setting and design

Community pharmacies belonging to the pharmacy practice research network (UPPER) of Utrecht University were invited to participate in this study. This network consists of 400 community pharmacies, which participate in research and other activities of the Department of Pharmaceutical Sciences on a regular basis. Of these, 15 responded positively and were enrolled in the study, serving a total population of approximately 150,000 patients. All participating pharmacies were equipped with dispensing records that could provide drug utilisation information, including date of dispensing, drug, dosage regimen, quantity supplied, type of prescriber, gender and date of birth of the patient. Since the majority of patients in the Netherlands are registered with only one community pharmacy, independently of prescriber, pharmacy records are virtually complete with regard to prescription drugs (12).

Patients received a questionnaire six months after presenting with a first prescription for an antidepressant. Guidelines recommend a minimum six months duration of treatment, which means that the information on use should remain with patients during that period as well. For that reason patients were asked to give their views six months after start of treatment. Furthermore, in order to obtain insight in patients' information needs, it was perceived as important that patients could consider their experiences with antidepressant drug taking during a certain period of time. Ethics committee approval at this time was not required in the Netherlands for this type of study. Non-responders were not informed at a personal level of their prescription data being used, but at the pharmacy level, being the pharmacy providing anonymised prescription data for research purposes. Prescription data from patients who objected to this procedure were excluded from the database.

Patient recruitment

Patients aged between 18 and 80 years, who received a first prescription of a second-generation antidepressant (serotonin-reuptake inhibitor (SSRI), venlafaxine or mirtazapine), between February 2004 and June 2004, could be included in the study. Exclusion criterion was use of any antidepressant within two years before the start of the study antidepressant.

Based on the inclusion and exclusion criteria, potential patients were selected through the pharmacy information and administration systems in January 2005.

Date of inclusion was between 180 and 270 days after patients' first prescription. The pharmacists sent the pharmacy records to the investigators, who selected a random sample of 25 eligible patients per community pharmacy. In turn, the pharmacies verified these patients by checking whether they had a medication history of at least two years, moved or died, leaving a total of 295 patients for inclusion. These patients received a pre-tested questionnaire through mail. Patients were asked to complete and return the questionnaire to the study coordinator within two weeks.

Questionnaire

Since we were not aware of a validated questionnaire regarding education and counselling in relation to the pharmacy, we developed our own. The topics were based on a validated questionnaire on satisfaction with information about medicines (SIMS) (13), and studies addressing the relation between patient information and antidepressant adherence (3), and education and counselling by pharmacies (2, 10). The way patients were informed by the pharmacy at the first prescription was determined by asking patients whether they received either written information only or verbal information in addition to written information. The questionnaire was pre-tested among a group of 20 patients.

Outcomes

Primary outcome measures were patients' views on the quality of patient information at the pharmacy and on the role of the pharmacy in patient education and counselling. To assess patients' views on the quality of patient information 22 questions were used. Four questions measured patients' views on written information, nine measured patients' views on verbal information and nine assessed patients' views on their own knowledge regarding the use of antidepressants. The questions on written and verbal information were coded on a scale of 1 to 5, ranging from strongly disagree (1) to strongly agree (5). The scoring of one question was reversed because of the negative formulation of the question. The questions on patients' knowledge were coded on a scale of 1 to 5, ranging from very insufficient (1) to very good (5). The outcomes of the questions are presented as a mean score, together with the standard error of the mean (SEM) and the range of the individual scores. Finally, five questions assessed patients' views on the role of the pharmacy in patient education and counselling. The response categories of these questions can be seen in Table 3. The outcomes of the questions are presented as percentages of the total number of patients.

Secondary outcome measures were duration of use and the number of antidepressant prescriptions, which were extracted from the pharmacy information and administration systems. Duration of use was defined as the time between the

dispensing date of the first prescription and the theoretical end date of the last prescription (dispensed within the study period of 180 days). The duration of use was cut off at 180 days. The number of prescriptions was defined as the number of prescriptions dispensed during the study period of 180 days. Treatment was considered to be discontinued when a prescription was not followed by a repeat antidepressant prescription within four weeks after the theoretical end date of that prescription. Switching to another antidepressant was considered as continuation of treatment. In the Netherlands it is standard practice to dispense a 14 day supply for new prescriptions. Subsequent prescriptions are usually for a 30 day supply. Analysis categories were based on this standard practice.

Data analysis

Descriptive statistics were used for the quality of patient information variables and the variables related to the role of the pharmacy. In addition, the non-parametric Mann-Whitney U test was used to analyse the skewed interval outcome variables, and the Chi-square test was used to analyse the categorical outcome variables. The Mann-Whitney U test was used to compare patients' views on written information and patients' views on the own knowledge of antidepressant use (as dependent variable), between patients who received written information only and patients who received both written and verbal information (grouping variable).
Baseline characteristics (age, gender, type of prescriber, type of antidepressant and use of concomitant medicines) were compared using the Chi-square test between patients who received written information only and patients who received both written and verbal information. The Fisher's exact test was used in case the conditions of the Chi-square test could not be fulfilled. The Mann-Whitney U test was used to compare the mean duration of use and the mean number of prescriptions (as dependent variables) between patients who received written information only and patients who received both written and verbal information (grouping variable). The responders' characteristics sex, type of prescriber, type of antidepressant and use of concomitant medicines were compared with those of the non-responders using the Chi-square test. In addition, the Mann-Whitney U test was used to compare the dependent variables age, mean duration of use and number of prescriptions (as dependent variables) between responders and non-responders (grouping variable). Data were analysed using the software programme SPSS version 14.0.

Table 1. Characteristics of patients receiving written information only versus patients receiving both written and verbal information

	Written information only (n=77)		Both written and verbal information (n=28)		
	n	%	n	%	p-value [a]
Gender					
male	20	26.0	11	39.3	0.19
female	57	74.0	17	60.7	
Age (years)					
18- 40	27	35.1	13	46.4	0.52
41- 60	30	39.0	8	28.6	
> 60	20	26.0	7	25.0	
Mean age (years±SEM)	48.0 (1.7)		46.0 (2.9)		
Prescribing physican					
general practitioner	72	93.5	22	78.6	0.06
psychiatrist	5	6.5	6	21.4	
Type of antidepressant					
citalopram	28	36.4	9	32.1	0.21
paroxetine	25	32.5	5	17.9	
venlafaxine	7	9.1	6	21.4	
other	17	22.1	8	28.6	
Concomitant medicines					
use of benzodiazepines	35	45.5	10	35.7	0.37
use of other psychiatric medication	4	5.2	2	7.1	0.70
use of non-psychiatric medication	57	74.0	15	53.5	0.04
no concomitant medicines	10	13.0	9	32.1	0.02

a p-values assessed using Chi-square test comparing patients who received written information only vs patients who received both written and verbal information. The Fisher's Exact test was used in case the conditions of the Chi-square test could not be fulfilled (i.e. prescriber characteristics).

Results

A total of 107 (36.3%) patients completed and returned the questionnaire. Two patients were excluded for claiming they didn't receive any information at their pharmacy, leaving 105 patients to be included in the analysis. Analysis of the responders and the non-responders (n=188) revealed significant differences between the two groups. The response group was older in age (mean age 47.4 vs 42.4 non-responders), had a longer duration of use (131 vs 84 days non-responders), received more prescriptions during the study period (5.5 vs 4.4 non-responders) and had their antidepressant less often prescribed by a psychiatrist (10.5 vs 23.4%). The responders and non-responders showed no difference in gender, type of antidepressant used and use of concomitant medicines.

Of the responders, 77 (73.3%) patients said they had only received written information at their first prescription at the pharmacy, while 28 (26.7%) patients indicated that they had received both written and verbal information. With respect

Table 2. Patients' views on the quality of information at the pharmacy. Patients receiving written information only versus patients receiving both written and verbal information.

	Written information only (n=77 [a])			Written and verbal information (n=28 [a])			
	Mean score	SEM [b]	Range	Mean score	SEM [b]	Range	p-value [c]
Written information questions [d]							
The information was useful	4.36	0.08	1-5	4.52	0.11	4-5	0.33
The information was understandable	4.28	0.06	3-5	4.30	0.13	3-5	0.73
I was satisfied with the information	4.19	0.07	2-5	4.18	0.14	2-5	0.92
The information added something to my knowledge	3.76	0.10	1-5	4.14	0.17	2-5	0.04
Verbal information questions [d]							
The information was useful				4.04	0.15	2-5	
The information was understandable				4.23	0.14	2-5	
The information added something to my knowledge				3.63	0.17	2-5	
I missed some information [e]				3.43	0.23	1-5	
The employee was competent				4.00	0.12	3-5	
I had the opportunity to ask my questions				4.13	0.13	3-5	
They spoke to me in a kindly manner				4.42	0.10	4-5	
They took my privacy into account				3.88	0.17	2-5	
I was satisfied with the information				3.92	0.16	2-5	
Patients' views on own knowledge [f]							
What the medicine is for	4.56	0.09	2-5	4.36	0.20	1-5	0.33
What it does	4.15	0.12	1-5	4.15	0.20	2-5	0.91
How to use your medicine	4.73	0.08	2-5	4.48	0.13	3-5	0.02
How long it will take to act	4.39	0.12	1-5	4.04	0.22	2-5	0.11
How long you need to be on your medicine	4.01	0.14	1-5	3.44	0.26	1-5	0.06
How to stop taking the medicine	3.70	0.16	1-5	3.54	0.26	1-5	0.56
Which symptoms may occur after stopping the medicine	3.33	0.16	1-5	3.22	0.27	1-5	0.72
Whether you can drink alcohol whilst taking the medicine	4.07	0.14	1-5	4.07	0.21	2-5	0.88
Whether the medicine has any side effects	3.97	0.13	1-5	3.44	0.26	1-5	0.08

a Not all questions were completed by all patients
b SEM: Standard Error of the Mean
c Mann-Whitney U test was used to compare the scores of the patients receiving written information only versus patients receiving both written and verbal information
d Scale meanings: strongly disagree (1) to strongly agree (5)
e The scoring was reversed because of the negative formulation of the question
f Scale meanings: very insufficient (1) to very good (5)

to the written information, 30 (28.6%) patients indicated they received a package insert only, while 75 (71.4%) patients indicated they had received a personalised information leaflet as well.

Table 1 shows the baseline characteristics for the patients receiving written information only as well as the patients receiving both written and verbal information. There were no differences between both groups for age, gender and type of antidepressant used. However, patients who received written information only used concomitant non-psychiatric medicines more frequently, compared to patients receiving both written and verbal information. In addition, patients who

Table 3. Patients' views on the role of the pharmacy in education and counselling

	n	%
Do they ask for your experiences with your medicine at the pharmacy?		
yes	9	8.6
no	96	91.4
Do you feel the need to discuss your experiences with the medicine with someone?		
yes	75	71.4
no	30	28.6
The pharmacy is an important source of information for me.		
agree	57	54.3
not agree	41	39.0
not completed	7	6.7
Who are the most suitable people for informing you on the medicine? (more answers possible)		
prescriber	95	90.5
pharmacist	24	22.9
pharmacy technician	13	12.4
not completed	3	2.9
Which people would you like to discuss your medicine with? (more answers possible)		
prescriber	84	80.0
pharmacist	13	12.4
pharmacy technician	10	9.5
other	33	31.4

received both written and verbal information tended to be more likely to have their antidepressant prescribed by a psychiatrist. Patients who had their antidepressant prescribed by a psychiatrist less often used non-psychiatric medication (27.3% vs 73.4% of the general practitioners' patients).

Table 2 presents the mean scores of patients' view on the quality of patient information received at the pharmacy for both groups of patients, i.e. patients receiving written information only and patients receiving both written and verbal information. Patients' views on the quality of written and verbal information supplied at the pharmacies were positive. The mean scores for written information for all patients (n=105) ranged between 3.9 and 4.4. The mean scores for verbal information ranged between 3.4 and 4.4. In their own opinion, patients were fairly knowledgeable about their antidepressant therapy as well. The mean scores of patients' views on their knowledge for all patients ranged between 3.3 and 4.7. For two items, there were significant differences between patients receiving written information only and patients receiving both written and verbal information. Patients who received both written and verbal information were more positive about the statement "The written information added something to my knowledge" and more negative about their own knowledge regarding antidepressant use, i.e. "How to use your medicine". In addition, patients who received both written and

Table 4. Duration of use and number of prescriptions. Patients receiving written information only versus patients receiving both written and verbal information.

	Written information (n=77)		Both written and verbal information (n=28)		p- value [a]
	n	%	n	%	
Duration of use (days)					
0-15	5	6.5	4	14.3	
16-45	11	14.3	1	3.6	
46-180	22	28.7	10	35.7	
>180	39	50.5	13	46.4	
Duration of use (mean±SEM)	133 (7.2)		127 (12.2)		0.73
Number of prescriptions					
1	9	11.7	5	17.9	
2	10	13.0	0	0	
3-5	22	28.6	10	35.7	
>5	36	46.8	13	46.4	
Number of prescriptions (mean±SEM)	4.9 (0.3)		4.7 (0.4)		0.76

a p-values assessed using Mann-Whitney U test comparing patients who received written information only versus patients who received both written and verbal information.

verbal information tended to be more negative regarding the knowledge items: "How long you need to be on your medicine" and "Whether the medication has any side effect".

Table 3 presents the outcomes of patients' views on the role of the pharmacy in patient education and counselling. The majority of patients (71.4%) reported that they feel the need to discuss their experiences with the medication. Most patients (80.0%) prefer to discuss their medication with the prescribing physician. The outcomes of the other questions also indicated that patients attribute more importance to their prescribing physician than to the pharmacist. In spite of the outcomes of the former questions, still 54.3% of the patients reported seeing the pharmacy as an important place to get medication-related information.

Table 4 shows the duration of use and the number of prescriptions for the patients receiving written information only versus patients receiving both written and verbal information. Within 180 days after the first prescription 52 (49.5%) patients discontinued their antidepressant treatment. Patients receiving both written and verbal information were more likely to discontinue their therapy after the first prescription, while patients receiving written information only were more likely to discontinue their therapy after two prescriptions (see Table 4). There were no further significant differences between both groups.

Discussion

This study shows that patients consider the quality of patient information given at the pharmacy at first prescription of an antidepressant to be quite positive. In addition, more than half of the patients regard the pharmacy as an important information centre. However, patients do not see an important role for the pharmacy in education and counselling on antidepressants. Ninety percent preferred to be informed by the prescribing physician. The same applies for the preference when discussing experiences with medication. There might be several explanations for the gap between the positive views on the quality of information and patients' need for information and discussing experiences on the one hand, and the limited role patients attribute to the pharmacy on the other. First, patients might be unfamiliar with the educational role of the pharmacy (10). Patients express considerable trust in their pharmacist, but are unaware what a community pharmacy can do apart from dispensing (14). Half of the patients do not know that they can ask the pharmacist for drug information (15). Thus, patients do not have great expectations and are easily satisfied with the information they receive. Second, many patients have a trusting therapeutic relationship with their physician, which often is absent with their pharmacist. Such a relationship appears to be a prerequisite for helping patients start or maintain antidepressant treatment (16). More than other chronic diseases, the nature of this disease requires ongoing professional support. Also, a lack of privacy at the pharmacy, which makes patients feel uncomfortable when receiving personal information, is considered to be an important barrier (7,10).

Patients receiving verbal information were more positive about the statement that written information added something to their knowledge, compared to patients receiving written information only. In addition, they were more negative about their knowledge on how to use the medicine. There might be several explanations. Patients receiving verbal information less frequently used concomitant non-psychiatric medicines, compared to patients receiving written information only. Patients who use less medication may be less familiar with medicines in general, and feel that they need more information. In addition, the severity of the disease might play a role. Patients who used less non-psychiatric medication were more likely to have their antidepressant prescribed by a psychiatrist, and thus more likely to be severely depressed. Physicians appear to provide less information to patients who present with major depression than to those with depressed mood (6). Finally, and most importantly, patients who receive information from more than one source, written as well as verbal, might be more capable to judge the information received and may be more critical about their knowledge regarding antidepressant medication (17).

We also studied whether verbal information in addition to written information given at the first prescription influenced the duration of antidepressant use. Only one quarter of patients indicated that they received verbal information along with the first prescription. These patients did not use their antidepressant any longer than the patients receiving written information only. The relationship between informing patients and adherence to treatment seems to be rather complex (7). Patients showed to use information in complex and sophisticated ways and information does not necessarily change patients' behaviour (18). Although some studies showed an effect of information on adherence to antidepressant medication, other factors like the doctor-patient relationship and experiencing adverse effects were contributing factors as well (1,2). Patients who received antidepressant information from different sources, including the pharmacist, were more adherent to their antidepressant regimen than patients who received information from fewer sources (17). Several pharmacy education and counselling programs have been developed and studied, but the results did not provide an obvious picture. A community pharmacy-based coaching program, including three coaching contacts and an informative take-home video, improved neither adherence to antidepressant regimens nor depressive symptoms (19). Nevertheless, the coaching program was evaluated as positive by the patients and had a positive effect on patients' drug attitude (20). Another study showed that pharmacist monitoring positively influenced both patients' satisfaction with their antidepressant medication and adherence (8). In our study, patients receiving both written and verbal information appear to discontinue their antidepressant more often after the first prescription in contrast to the patients receiving written information only. Informing patients of potential adverse effects has shown to increase the patients' awareness and reporting of adverse effects (21). The additional verbal information at the first prescription may indeed have increased patients' awareness of side effects and resulted in a decision not to take the medication.

Our findings must be seen in the light of several limitations. First, the selection of patients may have introduced a bias. Comparing responders to non-responders showed significant differences. The non-responders were younger, had their antidepressant more often prescribed by a psychiatrist, had a shorter duration of antidepressant use and received fewer prescriptions. Previous studies also showed differences between responders and non-responders (22). We cannot exclude that differences in these characteristics influenced our outcomes, which therefore may not be representative for all starting antidepressant users. There might also be a bias in the selection of pharmacies, which are all part of a research network. The participating pharmacies may be more committed to providing education and counselling, meaning that the general situation in practice would be even less

optimistic. However, we do not have any evidence for this. Third, patients were asked retrospectively, which might have introduced recall bias. The date of inclusion was at least six months after the patients' first prescription. It is very well possible that patients cannot remember whether they received verbal information. From the medical point of view, it is of vital importance that the patient retains the information during six months, as this is the minimum duration recommended for treatment. Memory lapses are described in literature as a frequent occurring problem with respect to patient education (23). Discrepancies were also shown between instructions that physicians report to communicate to patients and what patients remember being told (1). However, describing patients as forgetful and incompetent may be too easy and not in patients' interest. Non-compliance is often seen as failing on the part of the patient, and not as an intentional decision about medicine taking (23). Studies often consider increasing adherence to treatment the ultimate goal of providing information, and often do not take into account patients' satisfaction with treatment. However, from a patient's perspective, measuring patients' satisfaction with treatment might be more desirable than measuring adherence to treatment. It is striking that only a minority of patients in our study perceived a role for the pharmacist regarding verbal information, which is the issue that needs to be addressed. The lack of information about the content and the quality of the verbal information received by patients at the pharmacy might also be considered to be a limitation. However, focusing on the factual information received was not the aim of our study. Our intention was to provide insight in patients' perspectives on the information received, their knowledge regarding antidepressant use, and views on the role of the pharmacist. Patients' needs will definitely be influenced by personal experiences with the medication and process of communication. We believe that it is crucial to involve experiences with treatment in research in order to improve practice.

Several studies addressed the content and quality of information on antidepressants. Written patient information has been criticised for being too medico-centred (23,24). The content often centres on topics of importance to professionals, but may not reflect patients' actual needs. Grime and Pollock showed the distance between a medico-centred antidepressant information leaflet and patients' experiences with antidepressants (25). The leaflet did not address questions patients had, like the troublesomeness of side effects, physical addiction and decision making on starting or stopping treatment. A study by Garfield et al. identified information needs which were unmet at the start of antidepressant treatment, including the impact of adverse drug reactions on patients' lives, the very gradual process of recovery and addressing of the term dependency (5). Current information materials fail to give a balanced view of the effectiveness of treatments and ignore uncertainties, thereby

not supporting patients' involvement in treatment decisions (24). Improving leaflets to accommodate experiential patient knowledge would enable patients to engage in more concordant consultations with healthcare professionals (25).

Gardner et al. showed that community pharmacists express positive attitudes towards a wider role in the care of patients with depression, but their reported activities showed that they were doing little as intermediaries between patients and physicians (7). Pharmacists appeared most comfortable with providing information with first-time prescriptions, and less confident about discussing compliance issues with patients (9). The findings of our study confirm that patients perceive the pharmacists' role as limited, while patients simultaneously express a need to discuss their experiences with antidepressant taking. How can pharmacists accommodate patients' needs and how should the communicating process in the pharmacy be organised? The education process has to be an ongoing process, which cannot be accomplished in a single contact. Patients' feedback to professionals seems to be a key element in an optimal education process. Three monthly telephone calls from pharmacists providing structured education and monitoring improved the level of feedback to pharmacists, patients' knowledge and medication beliefs (26, 27). Such feedback from patients may help pharmacists identify and address patients' misconceptions, concerns, and progress with antidepressant treatment (27). This seems to be rather relevant as patients often have ambivalent feelings about taking antidepressants, which change over time and may prompt patients to stop taking the antidepressant (28). Pharmacists can enter into discussion with patients on their feelings and concerns about antidepressant taking. Giving patients the opportunity to discuss any concerns opens up the possibility to discuss adherence issues as a natural thing in the communication. In conclusion, the pharmacists' role needs to be more proactive, inquiring patients about their experiences with medication, stimulating patients to express concerns and supporting patients in their needs. They should not limit their role to providing information at the first prescription, but should be supportive during the whole treatment process. Pharmacists do have the tools to support patients in making an informed decision on either starting, continuing or stopping antidepressant use, and they should accept the challenge to do so.

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3 Execution of antidepressant therapy

3.1 Patients' health beliefs at start and during antidepressant treatment in general practice

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Abstract

Introduction

A growing body of evidence indicates that patients' beliefs are important to consider in understanding why patients do not follow prescriptions for antidepressants. This study aimed to investigate whether health beliefs and health status assessed at the start of antidepressant treatment are associated with subsequent drug taking behaviour, and to explore how health beliefs and severity of illness develop over time.

Methods

Eighteen Dutch community pharmacies participated in this observational study. Patients were followed until 26 weeks after presenting a first prescription for a second-generation antidepressant, prescribed by the general practitioner (GP). Patients completed a questionnaire at inclusion in the study, and at 6 and 26 weeks during follow-up. The outcome measure was the duration of antidepressant use. Explanatory measures included sociodemographic and medication characteristics, health beliefs and health status measures.

Results

Of all 110 patients, 8 (7.3%) did not initiate drug taking, 32 (29.1%) discontinued antidepressant use, 6 (5.5%) switched to different antidepressant medication, and 64 (58.2%) continued on the same antidepressant during follow-up. Compared to continuers, non-initiators had lower belief scores for impact of illness ($p=0.04$), patient's perception of whether GP thinks medication should be taken ($p<0.001$), patient's intention to take medication ($p<0.001$), and had a more negative attitude towards antidepressant medication ($p<0.01$). Furthermore, non-initiators were less severely depressed ($p=0.02$). Discontinuers and continuers did not differ in depression and anxiety severity at inclusion. However, discontinuers more often reported less specific symptoms as reason for use, such as fatigue and sleeping problems ($p=0.01$). Compared to continuers, switchers appeared to have higher illness severity at inclusion (depression: $p=0.04$, anxiety: $p=0.05$). During follow-up depression and anxiety severity improved for all treatment groups and reached the same level at six months.

Conclusion

Health beliefs and illness severity have an important influence on patients' decision about initiating, discontinuing or switching antidepressant drug taking. Patients' care can be improved by eliciting patients' beliefs about treatment and illness, and patients' perception of needing an antidepressant, before prescribing.

Introduction

Studies have shown that many patients stop taking antidepressants before the minimum six months duration recommended for treatment. About one-third of patients discontinue treatment within one month of starting, between one-third and half of the patients discontinue within three months, and more than half stop taking antidepressants in the first six months (1-7). Researchers have attempted to identify patient characteristics associated with discontinuation of antidepressant treatment, such as age, gender and ethnicity (1,2,8-11). Overall however, findings were disappointing. Correlations between adherence and sociodemographic variables, while sometimes statistically significant, are generally quite modest in magnitude. In addition, interventional strategies for helping patients to take their antidepressant medication as instructed were not successful. The effect on adherence to antidepressant treatment was, at best, only modest (12-16).

One of the major reasons for the lack of progress in practice lies in the relative absence of the perspectives of patients in research. Little is known about the ways patients think about their illness and treatment, their experiences with treatment and how these influence their behaviour. During treatment with antidepressants in daily practice patients face many problems which often lead to discontinuation of therapy (17,18). Furthermore, the passive role of patients in treatment decisions has been questioned. It has been suggested that patients make intentional decisions regarding their drug taking, based on their beliefs about the illness and its treatment (19-21). A growing body of evidence indicates that patients' beliefs are important to consider when trying to understand why many patients do not follow prescriptions for antidepressants (22-26). Building on this evidence, we conducted a prospective cohort study to follow patients during six months after having dispensed a prescription for a new antidepressant treatment. We aimed to investigate whether health beliefs and health status assessed at the start of antidepressant treatment are associated with subsequent drug taking behaviour, and to explore how health beliefs and severity of illness develop over time.

Methods

Design and setting

This prospective observational study was conducted between April 2006 and December 2007. Patients were followed until 26 weeks after dispensing a first-time prescription for a second-generation antidepressant. Twenty-eight Dutch community pharmacies were invited to participate in the study. Of these, 18 were enrolled in the study, serving a total population of approximately 180,000

patients. The participating pharmacies were located in a diverse range of urban and rural town settings. All participating pharmacies were equipped with a pharmacy information and administration system that could provide drug utilisation information, including the date of dispensing, drug, dosage regimen and quantity supplied. Since the majority of patients in the Netherlands are registered with only one community pharmacy, independently of prescriber, pharmacy records are virtually complete with regard to prescription drugs (27).

Patients

Patients aged over 18, presenting a first-time prescription for a second-generation antidepressant (selective serotonin-reuptake inhibitor, venlafaxine or mirtazapine) could be included in the study. The antidepressant had to be prescribed by a general practitioner (GP), and patients could not have used any antidepressant in the year before the dispensing date of the study antidepressant. The study was approved by an independent medical ethics committee, the METOPP (Medisch-Ethische Toetsing Onderzoek Patiënten en Proefpersonen) located in Tilburg, the Netherlands. All participants provided informed consent. The investigators anonymised patient information, and contact information (name, address and telephone number) was destroyed after the patients completed the study.

Procedures

Patients presenting a first antidepressant prescription at the pharmacy were asked by pharmacy staff to participate in the study. Patients who were willing to participate received a patient information letter, consent form and questionnaire. To reduce the possibility that participating in the study influences drug taking behaviour, the information letter described the purpose of the study in general terms, i.e. 'exploring experiences with antidepressant treatment'. The questionnaire was pre-tested among a group of 15 volunteers of varying ages and levels of education to establish feasibility and comprehensibility. As a result of the pre-test some minor changes in wording and the sequence of questions were made. Patients were asked to complete the questionnaire before start of medication, and to return it to the investigators within one week. Pharmacy staff faxed patient contact information to the investigators for further contact during the study. Subsequently, patients were contacted by phone at 1 and 16 weeks, and received a questionnaire through mail at 6 and 26 weeks after the date of inclusion. The inclusion date was defined as the date of dispensing the first-time prescription. Pharmacy staff was asked to register some characteristics (patient age and sex, type of antidepressant dispensed) of the patients not able or willing to participate. Non-participants were also asked for permission to provide drug dispensing data for comparing participants and non-participants.

Duration of antidepressant use

At each contact, 1, 6, 16 and 26 weeks after inclusion, patients were asked about their treatment status (i.e. whether they used antidepressant medication), and the reason for changes in treatment, if applicable. The length of time during which the patient used antidepressant medication was defined as the period between the first and last dose taken. It was assessed as reported by the patient. Data from the pharmacy information and administration systems were used to compare and confirm the length of use.

After having completed the study, patients were classified into four groups based on their drug-taking behaviour: (1) non-initiators (patients who were dispensed a study drug but did not initiate antidepressant use); (2) discontinuers (patients who started antidepressant use but discontinued any antidepressant treatment within the 26-week follow-up period), (3) switchers (patients who started antidepressant use, switched to different antidepressant medication but continued antidepressant use during the 26-week follow-up), and (4) continuers (patients who continued on the same antidepressant during the 26-week follow-up period).

Explanatory measures

Appendix 1 provides an overview of the different outcome measures assessed at each contact during the study period. The questionnaires at inclusion, and after 6 and 26 weeks included assessment of sociodemographic, health beliefs and health status measures. Information on medication use was extracted from the pharmacy information and administration systems.

Sociodemographic and medication characteristics

Next to age and gender, employment status, living situation, level of education and ethnic origin were included as sociodemographic characteristics. Education was divided into 3 categories: low (none/primary school), middle (secondary school) and high (college/university). Medication characteristics included concomitant use of benzodiazepines and number of co-medicines at time of inclusion, and previous use of psychiatric drugs for similar symptoms as asked for in the questionnaire.

Health beliefs

When designing the questionnaire we could not find a comprehensive questionnaire integrating patients' beliefs about treatment and illness, perceived treatment barriers and perceived norm of others. Therefore, we constructed our own belief measures. An extensive literature search on patients' perceptions of depression and its treatment was performed and several themes were identified. Thereupon, health beliefs were constructed based upon the social-cognitive variables proposed by the Theory of Planned Behaviour and the Health Belief Model. Appendix 2 shows the belief constructs and individual items assessed at inclusion. Cronbach's alpha was assessed for each belief construct. Impact illness, benefits of treatment, concerns

about treatment, and attitudes towards medication were also measured at 6 and 26 weeks after inclusion.

Health status measures

Health-related quality of life was assessed at inclusion using the Dutch version of the RAND 36-item Health Survey (RAND-36), previously tested and validated (28,29). To address the mental and physical components of this generic scale, the eight RAND-36 subscales were aggregated in two summary measures of physical and mental health, the Physical (PCS) and Mental (MCS) Component Summary (30). A score of 46 or less for the PCS and MCS represents a clear indication of physical and mental problems in the general population. The PCS and MCS have been demonstrated to be a reliable screening tool for physical and mental diseases (30,31). Severity of depressive and anxiety symptoms was assessed using a validated Dutch version of the Hospital Anxiety and Depression Scale (HADS) (32,33). This self-report questionnaire is developed to identify the presence and severity of mild depression and anxiety in non-psychiatric hospital outpatients. The total scores of each scale identify non-cases (7 or less), doubtful cases (8-10) and definite cases (11-21). The HADS was administered at inclusion, and after 6 and 26 weeks.

In the baseline questionnaire, patients were also asked for the main reason for antidepressant use. Depression, anxiety/panic disorder and obsessive compulsive disorder (OCD)/phobia are the officially approved indications in the Netherlands for the type of antidepressants studied. If the patient did not indicate any of these specific indications, the patient was considered to have a non-specific reason for use. Finally, patients were asked whether they received additional psychotherapeutic therapy, including all types of psychological or emotional counselling.

Analysis

For analysis of baseline explanatory measures, the groups of non-initiators, discontinuers and switchers were each compared with the group of continuers. Continuers were chosen as reference group as these patients have followed the recommended guidelines for practice (34,35). Differences in continuous measures (HAD–depression, HAD–anxiety, PCS and MCS) were examined using the Independent samples t test for normally distributed data. In case the conditions for the validity of the Independent samples t test were unmet (i.e. health beliefs, number of co-medicines) the Mann-Whitney U test was used. Differences in categorical variables were investigated using Chi-square test and Fisher's exact test in case the conditions of the Chi-square test could not be fulfilled.

For analysis of the within group changes in depression and anxiety severity for each treatment group (non-initiators, discontinuers, switchers and continuers) from inclusion until 26 weeks, Paired samples t test was used. One-way ANOVA was used to assess whether there were any overall differences between the four

treatment groups in depression and anxiety severity at 26 weeks after inclusion. To analyse the changes in health beliefs over time, we computed the change in belief scores for four constructs (impact illness, benefits and concerns about treatment and attitude towards treatment), by subtracting the 26-weeks follow-up score from the baseline score for each individual. To assess whether there were any overall differences in these changes in health beliefs between the four treatment groups, Kruskal-Wallis test was used. To further examine significant overall effects in the changes in health beliefs, Mann-Whitney U test was used to compare the changes in health beliefs for each of the groups of non-initiators, discontinuers and switchers, with the group of continuers. For analysis of changes in health status and health beliefs measures from inclusion until 26 weeks, only those patients who completed the 26-week questionnaire could be included. Data were analysed using the software programme SPSS version 14.0.

Results

Of the 207 eligible patients approached for the study, 110 (53.1%) agreed to participate and returned the baseline questionnaire. Of those returning the baseline questionnaire, 95 (86.4%) completed and returned the 26-week questionnaire. The reasons most frequently cited for not wanting to take part were unwillingness to participate in research in general (35.0%), survey being too complicated (14.4%), and feeling too distressed (6.2%). In addition, 7.2% of the non-participants had not yet decided whether to start drug taking and, therefore, were not interested to participate. For 34.0% the reason could not be ascertained. Participants and non-participants differed significantly in the length of antidepressant treatment. Non-participants were more likely than participants to not initiate or discontinue drug taking during the six months follow-up period, i.e. 53.6% versus 36.4% respectively ($p<0.001$). Participants and non-participants did not differ with respect to age, sex, type of antidepressant dispensed and co-medication.

Baseline sociodemographic, medication, health belief and health status measures

Table 1 shows the baseline characteristics of the non-initiators, discontinuers, switchers and continuers. Of all participants, 8 (7.3%) did not initiate drug taking, 32 (29.1%) started drug taking but discontinued antidepressant use within the six months follow-up period, 6 (5.5%) switched to different antidepressant medication but continued antidepressant drug taking during follow-up, and 64 (58.2%) patients continued on the same antidepressant medication during the entire follow-up period.

Table 1 Baseline characteristics of non-initiators, discontinuers, switchers and continuers [a]

	Non-initiators n=8 (7.3%)	Discontinuers n=32 (29.1%)	Switchers n=6 (5.5%)	Continuers n=64 (58.2%)
Sociodemographic measures				
Female gender (n,%)	5 (62.5)	20 (62.5)	5 (83.3)	42 (65.6)
Age (n,%)				
18-30	2 (25.0)	2 (6.3)	1 (16.7)	7 (10.9)
31-45	3 (37.5)	11 (34.4)	1 (16.7)	17 (26.6)
46-60	2 (25.0)	11 (34.4)	2 (33.3)	32 (50.0)
>60	1 (12.5)	8 (25.0)	2 (33.3)	8 (12.5)
Educational level (n,%)				
low	4 (50.0)	11 (34.4)	1 (16.7)	20 (31.3)
middle	2 (25.0)	11 (34.4)	3 (50.0)	21 (32.8)
high	2 (25.0)	10 (31.3)	2 (33.3)	23 (35.9)
Employed or in school (n,%)	5 (62.5)	19 (59.4)	3 (50.0)	39 (60.9)
Non-western ethnicity (n,%)	0	3 (9.4) *	0	0
Having a partner (n,%)	3 (37.5)	16 (50.0)	2 (33.3)	38 (59.4)
Living with others (n,%)	5 (62.5)	21 (65.6)	3 (50.0)	52 (81.3)
Medication related measures				
Type of antidepressant (n,%)				
paroxetine	2 (25.0)	8 (25.0)	2 (33.3)	25 (39.1)
citalopram	2 (25.0)	11 (34.4)	2 (33.3)	16 (25.0)
venlafaxine	1 (12.5)	5 (15.6)	1 (16.7)	8 (12.5)
other	3 (37.5)	8 (25.0)	1 (16.7)	15 (23.4)
Previous use of medication for symptoms (n,%)	2 (25.0)	10 (31.3)	3 (50.0)	17 (26.6)
Use of benzodiazepine at start (n,%)	0	13 (40.6)	2 (33.3)	20 (31.3)
Number of co-medicines at start (mean±SEM)	1.1 (0.7) *	2.3 (0.5) *	2.8 (1.1)	3.4 (0.4)
Health beliefs (mean±SEM)				
Impact illness	3.6 (0.3) *	4.1 (0.1)	4.2 (0.3)	4.2 (0.1)
Benefits of treatment	3.7 (0.2)	3.9 (0.2)	4.3 (0.3)	4.1 (0.1)
Concerns about treatment	3.5 (0.3)	3.2 (0.1)	3.3 (0.2)	3.1 (0.1)
Perceived norm partner	2.6 (0.6)	3.1 (0.3)	3.7 (1.3)	3.6 (0.2)
Perceived norm family/friends	2.5 (0.3)	2.9 (0.2)	3.0 (0.6)	2.9 (0.2)
Perceived norm GP	3.1 (0.3) *	4.4 (0.1)	3.8 (0.1) *	4.4 (0.1)
GP counselling and support	3.9 (0.4)	4.6 (0.2)	4.2 (0.4)	4.6 (0.1)
Attitude towards medication	3.1 (0.2) *	3.4 (0.1) *	3.4 (0.2)	3.7 (0.1)
Intention to take medication	3.4 (0.4) *	4.8 (0.1)	4.7 (0.2)	4.9 (0.0)
Health status measures				
Physical health (PCS) [b]	54.5 (2.7)	48.5 (2.0)	54.5 (5.0)	51.9 (1.2)
Mental health (MCS) [b]	31.0 (3.1)	28.4 (2.1)	17.8 (4.9) *	25.8 (1.1)
HAD scale – depression (n, %)				
non case (<8)	4 (50.0) *	7 (21.9)	0 *	9 (14.1)
doubtful case (8-10)	3 (37.5)	6 (18.8)	0	20 (31.3)
definite case (11-21)	1 (12.5)	19 (59.4)	6 (100)	35 (54.7)
HAD – depression total score (mean±SEM)	8.0 (1.7) *	11.6 (0.9)	15.0 (1.6) *	11.5 (0.5)
HAD scale – anxiety (n,%)				
non case (<8)	3 (37.5) *	6 (18.8)	0	6 (9.4)
doubtful case (8-10)	3 (37.5)	4 (12.5)	1 (16.7)	10 (15.6)
definite case (11-21)	2 (25.0)	22 (68.8)	5 (83.3)	48 (75.0)
HAD – anxiety total score (mean±SEM)	9.4 (2.3)	11.7 (0.6)	15.5 (1.6) *	12.2 (0.5)
Reason for use (n,%)				
specific indication (depression/anxiety/panic/ OCD)	6 (75.0)	22 (68.8) *	6 (100)	56 (87.5)
non-specific indication	2 (25.0)	10 (31.3)	0	8 (12.5)
Additional psychotherapy therapy at start	3 (37.5)	10 (31.3)	5 (83.3) *	23 (35.9)

The groups of non-initiators, discontinuers, and switchers were each compared with the group of continuers. The only difference found in sociodemographic characteristics refers to the patients of a non-western background among the groups of discontinuers; these patients were not present among the other groups. Furthermore, the non-initiators and discontinuers used less concomitant medication compared to the continuers. However, the major differences were found in the measures of patients' health beliefs and health status. Compared to continuers, non-initiators had lower belief scores for impact of illness ($p=0.04$), patient's perception of whether GP thinks medication should be taken ($p<0.001$), intention to take medication ($p<0.001$), and they had a more negative attitude towards antidepressant medication ($p<0.01$). Furthermore, non-initiators were less severely depressed (HAD total score, $p=0.02$), and less often identified as definite case of depression ($p=0.02$). In addition, non-initiators were less often identified as being a definite case of anxiety ($p=0.01$), whereas the mean HAD total anxiety score was not significantly lower in non-initiators ($p=0.07$), compared to continuers.
Discontinuers and continuers did not differ in depression and anxiety severity at inclusion. However, discontinuers more often than continuers reported less specific symptoms as reason for use ($p=0.01$; RR 2.9, CI 1.2 to 6.8), such as feeling down, fatigue and sleeping problems. In addition, discontinuers were more negative in their attitude towards medication than the continuers ($p=0.02$).
Finally, comparing the patients who switched to another antidepressant with the continuers, illness severity at inclusion was higher in switchers (HAD depression total score $p=0.04$, HAD anxiety total score $p=0.05$, MCS $p=0.04$), and switchers were more often identified as being a definite case of depression ($p=0.03$). In addition, switchers were less affected by their perception of the GP norm ($p=0.01$).

Changes in illness severity and health beliefs

Figure 1 presents the changes over time of depression and anxiety severity, and health beliefs about impact illness, benefits and concerns about treatment, and attitude towards medication during the six months follow-up period. Both depression and anxiety severity improved for all treatment groups. Analysis of the within groups changes over time, from inclusion to the end of the six months follow-up, showed significant improvements in illness severity for each treatment

a Non-initiators: patients who were dispensed a study drug but did not initiate antidepressant use; discontinuers: patients who started drug taking but discontinued antidepressant treatment during the 26-week follow-up; switchers: patients who started drug taking but switched to different antidepressant medication during follow-up; continuers: patients who continued on the same antidepressant during follow-up. The groups of non-initiators, discontinuers and switchers were compared with the group of continuers. Chi-square test and Fisher's exact test were used to compare the categorical measures. To compare continuous measures, Independent samples t test was used to examine PCS, MCS and HADS, and Mann-Whitney U test to compare health beliefs and number of co-medicines

b Based upon the RAND-36, the Physical (PCS) and Mental (MCS) Component Summary were assessed. Higher scores represent better functioning. A score of 46 or less for the PCS and MCS represents a clear indication of physical and mental problems

* p-value less than 0.05

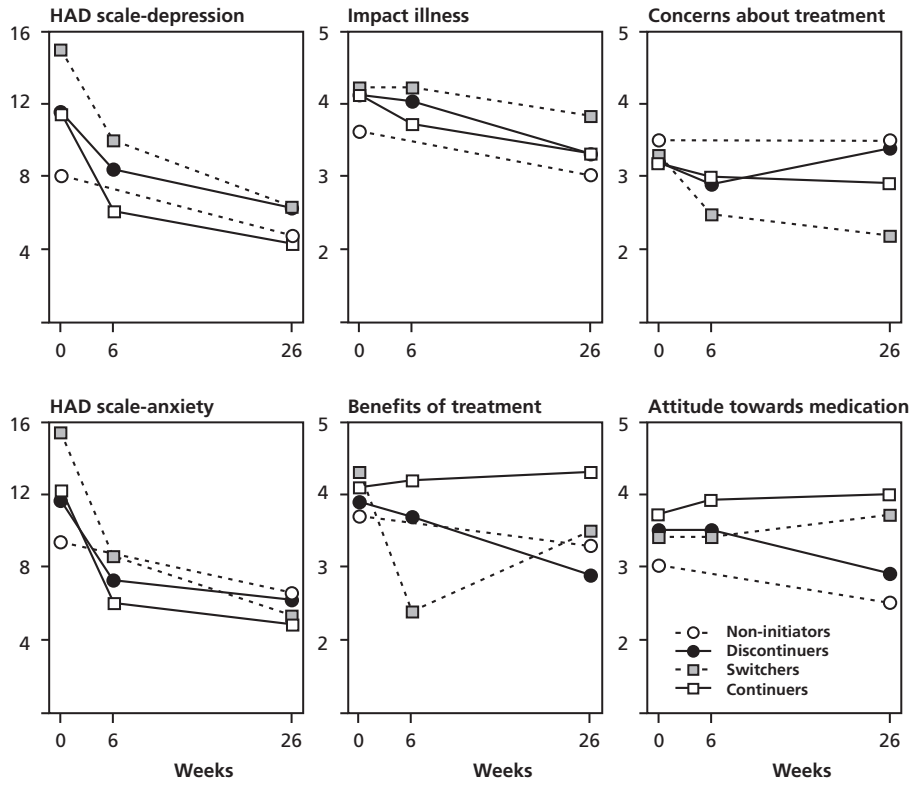

Figure 1 Changes in depression and anxiety severity and health beliefs (mean scores) during the six-month follow-up

Baseline: non-initiators n=8; discontinuers n=32; switchers n=6; continuers n=64
Week 6: discontinuers n=16; switchers n=5; continuers n=62
Week 26: non-initiators n=6; discontinuers n=21; switchers n=6; continuers n=62

group, except for anxiety in the group of non-initiators (p=0.21). At six months, depression and anxiety severity reached the same level for all treatment groups; when comparing the four groups overall, no significant differences in depression and anxiety severity (p=0.41 and 0.55 respectively) were found.

Health beliefs were influenced by patients' experiences over time. Comparing the changes in beliefs scores between the four treatment groups overall, from baseline to the end of the six months follow-up, revealed significant differences; the changes over time in benefits of treatment ($p<0.01$), concerns about treatment ($p<0.01$), and attitude towards antidepressant treatment ($p<0.001$) differed between the groups. To further examine the changes in the three belief constructs that were significant in the overall test, non-initiators, discontinuers, and switchers each were compared with the group of continuers. The changes in benefits of treatment from baseline to six months, were found to be significantly different between discontinuers and continuers ($p<0.001$); beliefs about perceived benefit of treatment decreased

Table 2 Reasons for not initiating, discontinuing or switching antidepressant drug taking [a]

Non-initiators (n=8)	Discontinuers (n=32)				Switchers (n=6)
	Within 2 weeks (n=14)	Between 2 and 6 weeks (n=4)	Between 6 and 16 weeks (n=10)	Between 16 and 26 weeks (n=4)	
Aversion towards medicine use (4) Fear of side effects (3) Feel fine, need no medicine (1)	Side effects (9) Feel fine, need no medicine (2) Unknown (3)	Side effects (2) Lack of effect (1) Unknown (1)	Side effects (2) Feel fine, need no medicine (5) Lack of effect (2) Unknown (1)	Feel fine, need no medicine (2) Both side effects and lack of effect (1) Unknown (1)	Side effects (3) Lack of effect (2) Both side effects and lack of effect (1)

a Non-initiators: patients who were dispensed a study drug but did not initiate antidepressant drug taking; discontinuers: patients who started drug taking but discontinued antidepressant treatment within 26 weeks after start; switchers: patients who started drug taking but switched to different antidepressant medication within 26 weeks after start

in discontinuers over time. The changes in the concerns about treatment beliefs were significantly different for discontinuers as well as switchers, compared to continuers ($p=0.05$ and $p<0.01$ respectively); concerns about treatment decreased in switchers whereas concerns increased in discontinuers. The changes in attitude towards medication were found to be significantly different for both non-initiators and discontinuers, compared with continuers ($p<0.01$ and $p<0.001$ respectively); the positive attitude towards medication decreased in non-initiators as well as discontinuers over time.

Reasons for not initiating, discontinuing and switching

Table 2 provides an overview of the reasons for not initiating, discontinuing and switching the initial antidepressant medication. Aversion towards medicine use and fear of side effects were main reasons for not initiating antidepressant drug taking. The occurrence of side effects was the main reason for discontinuing use within the first weeks of treatment, while from six weeks on most patients cited that they felt better and believed they do not need treatment anymore. Reasons for switching to different antidepressant medication were both side effects and lack of effect.

Discussion

This study showed that patients' health beliefs as well as illness severity have an important influence on patients' decisions about treatment, being either not initiating, discontinuing, switching or continuing antidepressant treatment. Beliefs about treatment changed over time. The initial differences in treatment beliefs between the groups increased during the six months follow-up, while severity of illness decreased to the same level in all patient groups during this period. We suggest four typical patient drug taking profiles. Patients who collect the antidepressant medication but do not start drug taking, the non-initiators, have the most distinct

profile. The non-initiators initially experience less severe symptoms, have a rather negative attitude towards medication, and tend to have stronger concerns about side effects. They are generally not very much affected by the perceived norm of the GP, and tend to perceive GP counselling and support as more negative. When collecting the medication, the non-initiators do not intend to start drug taking. Discontinuers, patients who discontinue drug taking within six months, had at the start the same level of symptoms as the continuers. There is, however, a discrepancy in their perception of symptoms. Discontinuers are more likely to report less specific symptoms as reason for use rather than depression or anxiety, and have a more negative attitude towards antidepressant medication. Patients who switch to different antidepressant medication are the ones who experience the most severe symptoms at the start and all cite depression, anxiety or OCD as reason for use. Switchers generally seem less affected by the perceived norm of their GP. Finally, the continuers' profile, i.e. patients who continue on the initially prescribed antidepressant during at least six months. Continuers experience relatively high levels of symptoms, are very much affected by the perceived norm of the GP and were rather positive about GP counselling and support. Their attitude at the start was mostly positive and when collecting the first prescription their intention to take antidepressant treatment was highest of all.
Treatment beliefs change over time. Continuers and switchers are likely to develop more positive beliefs during treatment, while their concerns about treatment decrease. Non-initiators and discontinuers are more likely to develop more negative beliefs about treatment over time. Overall, the differences between the users and non-users of antidepressant medication, which were already present at start, become more pronounced over time.

Over one in three patients did not initiate treatment or discontinued drug taking without switching to a second antidepressant. Although this is not in accordance with guidelines that recommend continuation of treatment for at least six months following remission of symptoms (34,35), not starting or discontinuing treatment was not disadvantageous with respect to the outcome measure of symptom severity, assessed at six and twenty-six weeks. It was remarkable that, whether or not treated with antidepressants, the severity of symptoms decreased in both users and non-users to levels below the threshold for depression or anxiety. Aikens et al. described a similar phenomenon (22). They found that patients who discontinued treatment were more sceptical of treatment at the start, whereas they were less impaired nine months later, compared to patient who continued treatment. They suggest that in some cases patient scepticism might mark a subgroup of patients who have a good short-term prognosis. We cannot dismiss either the possibility that the continuers in our study would have been more impaired when not having used antidepressant

medication for six months. Even though it does not seem to make much difference whether patients do not initiate or discontinue treatment with respect to the clinical outcome, beliefs about treatment are influenced negatively. It is important to realise that this may occur because negative beliefs may influence patients' trust in healthcare professionals and their attitude towards future treatment.

Another relevant issue we would like to discuss is the finding that a considerable number of patients received prescriptions, while they did not meet criteria for depression or anxiety. Prescribing antidepressants in these cases does not seem to be evidence based. Unfortunately, we are not aware of the GPs reasons to prescribe an antidepressant. GPs' decisions about whether an antidepressant would be an appropriate form of treatment are shaped by a set of rules based on clinical and social criteria (36,37). They seem to use non-specific clinical cues such as distress and impairment, as well as their knowledge of the patient, in diagnosing depression (38). Although GPs do not easily prescribe antidepressants, they may feel inclined to address patients' functional impairment which is also associated with mild depressive symptoms and emotional problems (39). However, it would be appropriate for GPs to ask patients how they interpret their symptoms and whether they believe an antidepressant would be helpful in treating the symptoms. This seems particularly relevant for discontinuers. Although discontinuers and continuers in our study were comparable in severity of their symptoms, the discontinuers more often reported less specific reasons for use, such as feeling down, fatigue, sleeping problems and thoughts running through the head. Apparently, patients who label their symptoms with a less specific term, are less likely to accept treatment. The relevance of determining how patients define their symptoms has also been shown to be crucial in patients who collect only a single antidepressant prescription at the pharmacy (7).

The present study confirms the evidence from other studies that patients' beliefs influence how patients use antidepressant medication. A study in predominantly male primary care patients with depression, found beliefs regarding perceived need treatment, the efficacy of treatment and beliefs about treatment barriers, to be predictive for initiating and adhering to antidepressant medication (24). Favourable attitudes towards antidepressant medication have been shown to be predictive of sustained adherence (22,25). Specific concerns about the long-term effects of taking antidepressants and about becoming dependent on antidepressants are associated with self-reported adherence (23,26). In addition, the mentioned study by Hunot et al. in patients newly issued with a prescription for antidepressants shows that a preference for alternative treatment acts as a significant barrier to

adherence (26). However, in contrast to this study, we showed illness perceptions to predict antidepressant non-use.

The strength of our study is that we provided prospective longitudinal data on patients starting a new treatment with antidepressants, and therefore could assess changes in patients' health beliefs and severity of illness over time. To our knowledge, no other studies have shown the development of treatment beliefs and severity of symptoms in a natural treatment setting. One of the major limitations of our study is bias due to selection of the study participants. Given the impaired situation at inclusion, often described as one of distress and hopelessness, it is understandable that patients have difficulty participating in research. Only half of the eligible patients agreed to participate. Comparison between participants and non-participants revealed that participants were more likely to initiate and continue drug taking during follow-up. Therefore, participants in our study may not be representative for all patients being treated in general practice. Patients willing to participate in research may have more positive beliefs about treatment and be more likely to accept medication. This suggests that current practice of patients receiving prescriptions for subtreshold depression and anxiety, and patients who do not prefer antidepressants for treating their symptoms, might be more unfavourable than shown in our study. Another limitation is the limited number of patients we were able to include. Due to the low number of patients, particularly in the groups of non-initiators and switchers, we failed to establish treatment concerns as a predictive factor. This in contrast to previous studies which were discussed above (23,26). Nevertheless, we have found several further interesting associations between patients' health beliefs and how patients use their medication.
We conclude that health beliefs and illness severity have an important influence on patients' decisions about initiating, discontinuing or switching antidepressant drug taking. Whether or not treated with antidepressants, patients showed similar patterns of depression and anxiety improvement. Patients' care can be improved by eliciting patients' beliefs about treatment and illness, and patients' perception of needing an antidepressant, before prescribing.

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Appendix 1 Overview of outcome measures assessed during the study period

Measure	Inclusion questionnaire	Week 1 phone contact	Week 6 questionnaire	Week 16 phone contact	Week 26 questionnaire
Sociodemographic characteristics	x				
Medication characteristics [a]	x				
Health beliefs					
Impact illness	x		x		x
Benefits of treatment	x		x		x
Concerns about treatment	x		x		x
Perceived norm partner	x				
Perceived norm family/friends	x				
Perceived norm GP	x				
GP counselling and support	x				
Attitude towards medication	x		x		x
Intention to take medication	x				
Health status					
Physical health (PCS)	x				
Mental health (MCS)	x				
HAD scale – depression	x		x		x
HAD scale – anxiety	x		x		x
Reason for use	x				
Additional psychotherapeutic therapy	x				
Treatment status (and reason for changes, if applicable)		x	x	x	x

a Information on concomitant medication (use of benzodiazepines and number of co-medicines at inclusion) was extracted from the pharmacy information and administration systems

Appendix 2 Health belief measures

Health belief items	Scale	Cronbach's alpha
Impact of illness (beliefs about the impact on functioning) • Because of my complaints I cannot function the way I want to • My complaints extremely bother me • I worry about my complaints	5-point Likert scale ranging from 1='strongly disagree' to 5='strongly agree'	0.78
Benefits of treatment (beliefs about the perceived benefits of the medication) • The medicine helps me to deal with my problems • The medicine makes me stronger so that I can better cope with my problems	5-point Likert scale ranging from 1='strongly disagree' to 5='strongly agree'	0.77
Concerns about treatment (beliefs about the negative effects of the medication) • There is a high risk of undesired effects when using the medicine • There is a high risk of undesired long-term effects of the medicine • This medicine can cause dependency when you use it for a long period of time • It is difficult to stop taking the medicine when you use it for a long period of time	5-point Likert scale ranging from 1='strongly disagree' to 5='strongly agree'	0.69
Perceived norm partner (patient's perception of whether the partner thinks medication should be taken) • My partner thinks it is important that I use the medicine • I am bothered by the view of my partner on taking the medicine • Regarding the use of the medicine I follow the advice of my partner	5-point Likert scale ranging from 1='strongly disagree' to 5='strongly agree'	0.81
Perceived norm family/friends (patient's perception of whether family or friends think medication should be taken) • My family/friends think it is important that I use the medicine • I am bothered by the view of my family/friends on taking the medicine • Regarding the use of the medicine, I follow the advice of my family/friends	5-point Likert scale ranging from 1='strongly disagree' to 5='strongly agree'	0.85
Perceived norm GP (patient's perception of whether the GP thinks medication should be taken) • My GP thinks it is important that I use the medicine • I am bothered by the view of my GP on taking the medicine • Regarding the use of the medicine, I do what my GP thinks is needed	5-point Likert scale ranging from 1='strongly disagree' to 5='strongly agree'	0.79
GP counselling and support (perception of GP counselling and support) • I think I receive sufficient counselling and support from my GP • My GP takes sufficient time to listen to my problems • My GP is really interested in my problems	5-point Likert scale ranging from 1='strongly disagree' to 5='strongly agree'	0.93
Intention to take antidepressant medication (behavioural intention to take the medicine) • I intend to take the medication the coming period • I intend to take the medication according to the instructions	5-point Likert scale ranging from 1='strongly disagree' to 5='strongly agree'	0.76
Attitude towards medication (overall opinion about taking antidepressants) I think that using this kind of medicine is: absolutely useless - very useful; very unpleasant - very pleasant; absolutely needless - absolutely necessary; very bad - very good	5-point semantic differential scale	0.80

3.2 The decision to continue or discontinue treatment: experiences and beliefs of users of selective serotonin-reuptake inhibitors in the first months. A qualitative study

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Submitted for publication

Abstract

Introduction

From the medical point of view, discontinuation of selective serotonin-reuptake inhibitors (SSRIs) within six months of starting treatment is considered problematic. So far, quantitative studies have not been able to explain the decision making process regarding discontinuation or continuation of SSRI treatment. The objective of this study was (1) to explore experiences and beliefs of SSRI users in relation to initiation and execution of treatment, and (2) to identify patterns of experiences and beliefs leading to discontinuation or continuation of treatment.

Methods

Patients aged over 18, who had started treatment with an SSRI prescribed by a general practitioner (GP) within the previous four months, and who obtained the SSRI for a minimum duration of use of two months, were selected. Eighteen patients were interviewed three months after starting SSRI treatment, nine of whom had discontinued (discontinuers) and nine continued (continuers).

Results

Considering similarities and disparities revealed two main patterns leading to either discontinuation or continuation of use. The disparities seemed to reach far beyond patients' health threat and the therapeutic effects of the drug. Rather, continuers were satisfied with the GP's role during initiation and execution of SSRI treatment, and fully trusted their decision. Continuers' attitude towards SSRI treatment was predominantly positive; they seemed to have little doubt about the necessity of using an SSRI, and hardly considered discontinuing for fear of relapse. Discontinuers, on the other hand, perceived the GP's role as limited, both during initiation and execution of SSRI treatment. They seemed to be less involved in decision making, and often appeared to have little confidence in their GP. Most discontinuers felt they lacked knowledge on SSRI use, and their attitude towards SSRI taking was rather negative. Discontinuers were often unconvinced about the necessity of using an SSRI, and appeared to have a strong desire to discontinue treatment.

Conclusion

Discontinuation of SSRI treatment under current suboptimal circumstances is not favourable for patients; GPs and other healthcare professionals could be more supportive during the first months of SSRI treatment by eliciting patients' considerations for continuing or discontinuing treatment.

Introduction

Many patients discontinue treatment with selective serotonin-reuptake inhibitors (SSRIs) long before the minimum six months' duration recommended for treatment. Approximately one-third of patients discontinue treatment within one month of starting; between one-third and half of patients discontinue within three months; and half to almost three-quarters stop taking antidepressants in the first six months (1-5). Different studies, often using a quantitative approach, have presented a range of factors involved in discontinuation of SSRI treatment (6). Yet these studies do not clearly distinguish between those discontinuing within the recommended half year treatment period. For the quantitative assessment of how patients take their prescribed medicines, Urquhart and Vrijens suggested considering three phases within the course of drug taking: acceptance of the treatment plan leading to initiation; execution of the drug regimen; and eventual discontinuation (7). For antidepressants it is most likely that the problems arising during the three phases of treatment – and the factors concerned – differ from each other. In light of new information and experiences acquired during the process, patients constantly reassess the decision to comply with the treatment plan (8). Interpretation of symptoms by the patient, beliefs about and experiences of medication, and perceptions of practitioner consultations are likely to influence the initiation of antidepressant use (9-11). During execution of treatment other issues may arise. Many patients experience side effects before they experience recovery from symptoms (12). Side effects may occur immediately after starting, and the burden can be rather big. After tolerating the difficult initial weeks, and once the antidepressant starts working, patients usually feel better. Yet, at this point, it appears that many patients decide to stop taking their SSRI.

From the medical point of view, discontinuation of antidepressants within six months of starting treatment is considered to be a problem, and improving adherence is deemed important in order to decrease the risk of a recurrence of symptoms and improve quality of life (13,14). However, so far the medical profession has not managed to improve discontinuation rates, and interventions that have been developed to prevent antidepressant treatment discontinuation have failed to demonstrate a clear benefit (15,16). One might conclude that quantitative studies have improved our knowledge but are not able to explain the whole complexity of medication-taking behaviour. Little is known about patients' views on SSRI taking and their decision making processes regarding either continuation or discontinuation within a few months of starting. A more in-depth view of the experiences and opinions of patients starting SSRIs is desirable in order to gain more understanding of the decision making process, which may be useful for physicians and pharmacists in order to reconsider their role in supporting patients.

We interviewed patients three months after the start of SSRI treatment, intending to (1) explore the experiences and beliefs of SSRI users in relation to acceptance and execution of treatment, and (2) to identify patterns of experiences and beliefs leading to discontinuation or continuation of treatment.

Methods

Setting and patients

Patients were recruited through seven community pharmacies in the north of the Netherlands. The pharmacists used automated pharmacy dispensing records to select potential patients. Patients aged over 18, who had started treatment with an SSRI prescribed by a general practitioner (GP) within the previous four months, and who obtained the SSRI for a minimum duration of use of two months, were selected. Patients were not allowed to have used an antidepressant in the year before the start of this SSRI treatment period. Since the majority of patients in the Netherlands are registered with only one community pharmacy, independently of the prescriber, pharmacy records are virtually complete with regard to prescription drugs (17).

Patients fulfilling the criteria were defined into two groups by one of the authors (JH): discontinuers and continuers. Patients were defined as a discontinuer when an SSRI prescription was not followed by a repeat prescription of the same SSRI within 30 days of the theoretical end date of the last prescription. Patients were defined as a continuer when a prescription was followed by a repeat prescription of the same SSRI within 30 days of the theoretical end date of that prescription. Our intention was to include only patients who used the SSRI for depression or anxiety related symptoms. However, we had no available information on diagnosis, and therefore at this stage of the study could not yet exclude patients who used the SSRI for other indications. Patients were phoned either by the pharmacist, or by one of the authors (JH) on behalf of the pharmacy. If patients were willing to participate, they received an information letter providing background information on the study. Ethics committee approval was not required in the Netherlands for this type of study. Patients were given several opportunities to consider the request to participate and to refuse participation in the study: namely at the moment of the phone call invitation, after having received the information letter, and before the start of the interview itself. Because patients might have discontinued treatment during the period between the initial contact and the moment of the interview, definitive assignment as either a discontinuer or continuer was based on patients' judgement of their treatment status at the moment of the interview.

Interviews

One of the researchers (JH) carried out all interviews after participating in training sessions conducted by an experienced teacher of interview skills. The interviews were held in patients' homes or in the pharmacy, depending on the patient's preference. The interviews lasted between 30 and 75 minutes. Each interview began by asking the patient to describe the way in which they came to start treatment with an SSRI. The interview was further guided by a list of topics, linked to the three phases of drug taking based on a paper by Urquhart and Vrijens: initiation of treatment, execution, and discontinuation of use (7). The list of topics was based on literature exploring patient related factors involved in discontinuation of antidepressants, and included: the health threat at the start of treatment; attitude towards disease and SSRI use; perceived effectiveness and side effects of the SSRI; communication with and counselling by healthcare professionals; knowledge of SSRI use; social support of family and friends; and considerations for continuing or discontinuing SSRI treatment (5,18-20).

Analysis

The interviews were audio-taped and notes were taken concurrently. The audiotapes were later transcribed verbatim. Potentially identifying information was removed from the transcript, and transcripts were assigned a code number. The data were analysed using a modified grounded theory approach (21). The authors studied the interview data to see which incidents, events, and activities could be identified, and continuously compared them with an emerging theme or category in an attempt to develop and inter-relate categories of information. These were discussed by the researchers to generate new insights inductively. All analysis was done by the first author (KvG) and an advanced graduate student (JH), and was facilitated by discussions with the other authors. The authors intended to describe the different domains that played a role during the first months of SSRI treatment as a chronological process based on the course of drug taking; namely starting with initiation of use, followed by execution and discontinuation of SSRI use (7). This was done for the overall group of discontinuers and continuers. Subsequently, for each phase similarities and disparities between discontinuers and continuers concerning the different domains were explored and described. The initiation phase is considered to start with patients presenting their symptoms to the physician, and to succeed when treatment is initiated; execution is the phase between initiation and discontinuation of treatment; and discontinuation refers to the act of discontinuing treatment.

Results

Fifty patients were selected and contacted. Of these patients, one was hospitalised, and twenty-eight refused to participate. Reasons for not participating included not seeing any benefits for themselves, a general unwillingness to participate in research, failure to present at the interview, and language difficulties. Twenty-one patients (43%) agreed to be interviewed. However, during the interview process three patients had to be excluded: two appeared to not be recent starters, and one used the SSRI for a different indication (premature ejaculation problems). Ultimately, interviews with nine patients who had discontinued SSRI use (discontinuers) and nine patients who were still using SSRIs (continuers) could be analysed. The mean age of the patients was 51 years, and 72% were female. The majority were married (78%), had a middle level of education (61%), and were unemployed or retired (67%). Nine patients used citalopram (50%), five paroxetine (28%), three fluoxetine (17%), and one fluvoxamine (6%). Seven patients (39%) used a benzodiazepine as a concomitant drug, mostly only during the first weeks of SSRI treatment. Table 1 shows the individual characteristics of the discontinuers and continuers.

Table 1 Characteristics of patients

Patient no.	Gender	Age	Marital status	Educational level	Employment status	Type of SSRI	Duration of SSRI use [a]	Concomitant benzodiazepine use
Discontinuers								
1	Male	83	Married	Middle	Retired	Paroxetine	2.5 months	No
2	Male	39	Divorced	Middle	Employed	Citalopram	2.5 months	No
3	Female	37	Married	Middle	Unemployed	Citalopram	3 months	No
4	Female	52	Married	Low	Unemployed	Fluoxetine	2 months	No
5	Female	19	Single	Low	Student	Paroxetine	3 months	No
6	Male	68	Married	High	Retired	Fluvoxamine	2 months	No
7	Male	41	Divorced	High	Unemployed	Citalopram	3 months	Yes
8	Female	62	Married	Middle	Unemployed	Paroxetine	3 months	No
9	Female	51	Married	Middle	Unemployed	Citalopram	3 months	Yes
Continuers								
10	Female	51	Married	Middle	Employed, part time	Citalopram	4 months	No
11	Male	62	Married	Middle	Retired	Paroxetine	3 months	Yes
12	Female	41	Married	High	Employed, part time	Citalopram	2.5 months	Yes
13	Female	47	Divorced	Middle	Employed	Fluoxetine	3 months	Yes
14	Female	60	Married	Low	Unemployed	Fluoxetine	2.5 months	Yes
15	Female	48	Married	Middle	Employed, part time	Citalopram	3 months	No
16	Female	34	Married	Middle	Unemployed	Citalopram	2 months	Yes
17	Female	64	Married	Low	Unemployed	Paroxetine	3 months	No
18	Female	67	Married	Middle	Unemployed	Citalopram	3 months	No

a For the discontinuers: time from initiation until discontinuation; and for the continuers: time from initiation until the moment of the interview

Initiation of SSRI use

While analysing the interview data from the moment patients presented their symptoms to the physician until treatment was initiated, the following domains emerged: health threat at start of treatment, previous experiences with antidepressant use, treatment decision making with GP, attitudes towards SSRI treatment, confirmation and explanation of the problem, and information on SSRI use.

Health threat at start of treatment

Prior to taking SSRIs, most patients described their situation as one of distress and hopelessness. All patients mentioned depression related symptoms, such as restlessness, bouts of crying or tearfulness, sleeplessness, loss of energy, and being easily irritated.

> *I felt very depressed and down. I was unable to settle down and do something. I started getting upset easily, even with my children. I felt fatigued and tense all the time; I didn't have the energy. (patient 3, discontinuer)*

Most patients also mentioned anxiety related symptoms, such as feeling anxious and having panic attacks.

> *For quite a while already I was suffering from anxiety and panic attacks. At some point it got out of control; I couldn't suppress it any more. I was truly afraid of my fears, and wasn't looking forward to anything. Even opening the mailbox felt like it was too much to handle. (patient 13, continuer)*

All patients had great difficulty functioning in everyday life, either at work or at home as a parent or partner, and often felt guilty about this.

> *What I would usually get done in a day now took me three days. That, in turn, made me feel guilty, and even more depressed. It felt as if I had failed; I just couldn't do it. (patient 15, continuer)*

Some patients were suddenly overtaken by the symptoms shortly before starting to take the SSRI; others had experienced the symptoms for a longer period of time, in some cases more than a year, and had tried to change their situation for some time before consulting their GP. However, at some point they all realised that they could not handle their problems themselves.

> *Until, at some point, you reach your limit, and then cross it. Just to avoid the constant thinking, the feeling of fear. That's when I realised this is it, I have to stop this. (patient 13, continuer)*

Previous experiences with antidepressant use

More than half of the patients did not have any previous experience with antidepressants. Seven patients, however, did have previous experience with SSRI use, positive as well as negative. Negative experiences were reported by four patients. These patients experienced a lack of efficacy, allergic reactions, side

effects like palpitations, diarrhoea, and nausea, and withdrawal symptoms during discontinuation. These patients had been prescribed a different type of SSRI this time, and emphasised that they would not have accepted the same one.

> *Years ago I was taking a similar medication, which gave me heart palpitations and diarrhoea. When I went to the GP I told him that in any case I didn't want those any more. I was simply afraid to start getting heart palpitations again. (patient 14, continuer).*

It was not clear, however, whether they all discussed their previous experiences with, and opinions about, a particular SSRI with their GP, and therefore whether the prescribing of another type of SSRI was an intentional decision of the GP based on patients' experiences.

> *During the first several weeks of using the previous medication I suffered quite a bit from side effects. At some point I no longer noticed its intended effect; the symptoms started to return. If the GP had prescribed that same medication again this time, then I might have decided not to take it. (patient 5, discontinuer)*

Although the negative experiences made patients reticent about the newly prescribed SSRI treatment, the new treatment received the benefit of the doubt.

> *I didn't believe it would work, as with the other antidepressant I hadn't noticed any improvement either. I reluctantly went along; now it has become very clear to me that it actually works. I was truly surprised by its effect. (patient 10, continuer)*

One patient experienced both positive and negative effects of previous treatment, but overall she judged treatment with the SSRI as positive. Through this experience she was able to recognise the depressive symptoms, which made her contact her GP at an early stage this time. She was also aware of side effects that might occur and knew that they would probably disappear after the first weeks.

> *I started getting specific symptoms that I recognised from before. It didn't seem like a good idea to let it get much worse, so I went back to our GP. Having used it before definitely helped: it makes it easier to explain certain side effects you might experience. You know it will all be just fine, if you give it some time. (patient 16, continuer)*

Two patients were solely positive about previous treatment with SSRIs. The SSRI improved their symptoms and made them feel better, while bothersome side effects did not occur. These patients indicated that this positive experience made it easier to consult the GP this time, and to discuss their problems.

> *I had used paroxetine before, several years ago. That had made me feel so much better. This time I again felt weird and awful, so I went to our GP. He said that since I had experience with using this medication, and it went well before, I got it again this time. (patient 17, continuer)*

Treatment decision making with GP

Ten patients indicated that it was the GP who offered to prescribe an SSRI. Seven of them reported that they had confidence in their GP, and were either convinced that there was no other option than accepting the prescription, or did not feel capable of finding another way.

> *I'm not the kind of person that takes a lot of medication, but if I have to, I will. Our GP is knowledgeable and he recommends this to me, so I will take it. (patient 11, continuer)*
>
> *He told me "This is better for you", so then I went ahead and started using it. Not really a conscious decision. You don't really know why, or for how long; you don't really know anything. If a GP can't explain to you why and what for, then you probably won't accept the medication he has prescribed as easily either. (patient 3, discontinuer)*

Three patients did not immediately accept the GP's offer for an SSRI prescription. They were rather shocked about receiving the diagnosis of depression and expressed a general aversion towards medicine use. They needed some more time and further advice from their GP, family, or friends to feel confident that SSRI treatment might be helpful in their situation.

> *I did know a bit about antidepressants and I definitely didn't want any of that. The doctor suggested it to me three times, and all three times I pushed it off. Eventually, when the situation got quite desperate, I gave in. (patient 7, discontinuer)*

In some cases GPs had to argue with patients in order to convince them to initiate use. The biochemical explanation of a serotonin shortage in the brain, and the argument that patients' problems were caused by factors out of their personal control, were regularly used by the GPs. The arguments were more or less convincing to the patients.

> *My GP explained that your brain produces certain chemicals that have to be in balance. That balance may be what I'm missing. If this pill makes me get my balance back then I would sell myself short if I don't take it, according to him. (patient 8, discontinuer)*

Five patients asked for an SSRI prescription themselves. They either had used an SSRI in the past, or read about SSRIs in the media. The GPs seemed to be supportive and granted patients' request for a prescription.

> *The doctor had first prescribed a "Benzo", but that made me feel quite groggy. There had to be a better alternative. That's when I read about Prozac, and brought it up myself. I felt the doctor was taking me seriously. (patient 13, continuer)*

For three patients the GP did not seem too involved in the treatment decision making. Two of them indicated that the SSRI was prescribed by the GP on the advice of another healthcare provider. The third patient always requests a prescription by phone, during periods of symptoms. All three patients indicated

that there was no communication with the GP about the medicine during this phase of treatment.

Attitude towards SSRI treatment

Having been prescribed the SSRI, patients expressed different kinds of feelings about the medicine. Although most patients had ambivalent feelings at that moment, weighing up these feelings seemed to result in either a predominantly positive or predominantly negative attitude towards SSRI use. Half of the patients had a predominantly positive attitude towards SSRI use. After a certain period of reflection, in the end they were all convinced that SSRI use was necessary and inevitable. Some patients did not seem to have any misgivings at all about starting an SSRI; it seemed relatively easy for them to make up their mind. They did not see any reason why, when having serious problems, they should not take a medicine which in their opinion has been proven to be effective and safe.

> *I don't have a problem with it, and don't feel weird about this kind of medication. Obviously I'd rather be healthy without medication, but if you can't live without then you have to take them. If the medication was bad then the GP wouldn't have prescribed if to me. (patient 17, continuer)*

In this context, a few patients indicated that it was relatively easy for them to accept the offer of treatment as they felt that emotional problems must be treated just like physical problems.

> *To me it's quite simple: a person with heart problems takes heart medication, so if there's a short-circuit in your brain which causes you to have too little serotonin, then you take fluoxetine. (patient 13, continuer)*

Fear of side effects and fear of dependency did not really seem to bother the patients with a positive attitude towards the SSRI. Although some of them mentioned these issues, at the same time they seemed to realise that adverse effects are a natural consequence of taking medicine. A few of the patients even considered the SSRI as mild and harmless, and seemed to play down the therapy by describing the physical appearance of the tablets, such as being just a small tablet to be taken just once a day.

> *Citalapram is a new medication with a lot less of that chemical. The pill also looks good. I used to take "Librax" which had a nasty green colour. This one is just a basic white. (patient 12, continuer)*

Half of the patients had a predominantly negative attitude towards SSRI use. The patients reported ideas and beliefs that were either related to their self-esteem, or more related to the use of the medicine itself. With regard to patients' self-esteem, handling problems on one's own strength, without the help of an SSRI, was a major issue for most patients. They felt it was a sign of weakness that they had to take a medicine to improve their situation. They felt guilty and ashamed of this.

I actually wanted to fix it myself. If you can resolve it without medication then you're part of the regular people, but now I no longer belong to that group. Taking medication means admitting failure. (patient 10, continuer)

In addition, several patients expressed the fear of being labelled as a person with a stigmatising emotional disorder.

I'm afraid to get labelled unstable. You generally get told to just get off your ass and do something about it, then it will be just fine. (patient 12, continuer)

A few patients were bothered by the idea that initiating SSRI use implies that they have a brain problem. They perceive a brain or emotional problem as more difficult to accept than a physical problem.

To me, cholesterol reducers are something different; that you can't really do anything about. In this you can't really either, but still… it's something that's in your brain. That's what makes it difficult for me to take medication. (patient 3, discontinuer)

A negative attitude was also based on ideas and beliefs related to the use of medicine itself. Some of the patients reported a general aversion towards medicine use, and felt medicines do not fit into their way of life. In addition, some considered SSRIs to be chemical and unnatural.

In principle I've always been against using medication. It's pure poison, it doesn't belong in your body. You have to give your body a chance to resolve itself as long as possible. (patient 6, discontinuer)

Patients also expressed concerns about side effects in general, about long-term effects on their brain and personality, and fear of dependency.

You can get dependent on SSRIs. When you stop using it the depression can return even worse. I believe you should use an antidepressant only temporarily. (patient 7, discontinuer)

Some expressed the belief that an SSRI does not tackle the cause of the problems. They realised that it is of crucial importance to identify the real cause of depression or anxiety, and to deal with it.

I always want to maintain control over my own life, but the medication dominates. The problem doesn't get treated. You become depressed for various reasons, and you have to do something about it. (patient 7, discontinuer)

Some patients also emphasised that they did not want to rely completely on the SSRI, but did want to use the SSRI as a resource to work with themselves.

It's just that bit of support that allows you to work at yourself. It's not a miracle pill, I definitely realise that. I hope in some time I can do without it, because I don't want to be hooked on it for the rest of my life. (patient 16, continuer)

Confirmation and explanation of the problem

Receiving an SSRI prescription made patients often reconsider their problems. For two patients it was a relief to receive a prescription. They perceived it as a

confirmation that their situation was really serious. It made it easier to tell others – at work, family, or friends – why they were not able to function in everyday life as they did before.

> *I was actually quite relieved when I got the medication. You are really sick and you're not just pretending. Your behaviour is no longer strange; it's okay now. If you have a broken leg, then everyone accepts that you can't move around. They'll come visit and you'll get flowers. But if they can't tell what your problem is, then you're just weak, lazy, or egocentric, then you're just not right. (patient 10, continuer)*

Other patients did not mention the confirmation of receiving a prescription as an important factor. However, several patients expressed a need for a certain acknowledgement of the fact that they are going through such a difficult time. They found it hard to have a problem which is not visible to the outside world, and would rather have a physical problem, such as a broken leg. These types of problems are considered to be out of your control, you do not have to blame yourself. Emotional problems, on the other hand, are considered to be caused by a person's own weakness, which means that they themselves should have a major role in solving it. Some patients were bothered by this feeling, which they considered to be the general public view.

> *My superior doesn't understand it. I'd rather have a broken leg, that would be easier. It's clearly visible to those around you, and you know it will heal. I would also have a legitimate reason not to function well. Now I sort of feel that I'm to blame, that I'm blocking the healing process. (patient 12, continuer)*

Some patients emphasised that they did not feel that they had depression. They would rather label their symptoms with a less loaded term, such as burn-out or hormonal imbalance.

> *I kept insisting it wasn't a depression I was feeling, and I still don't like it. (patient 12, continuer)*

For most patients it seemed to be essential to gain more understanding of the cause of their problem and to find some kind of explanation. Six patients were told that their problems were caused by a serotonin deficiency in the brain, and that SSRIs would address this imbalance. For three of them, this explanation was helpful in accepting the condition as well as the treatment.

> *I was glad this guy on the radio explained it this way, that when you're depressed your brain has too little of a certain chemical. I had heard that before and realise there are contradicting theories. But now it's quite convenient for me to believe this particular one. (patient 10, continuer)*

However, the serotonin deficiency explanation was not convincing for all.

> *That's why my view on this medication has changed, but I'm not entirely convinced yet. (patient 8, discontinuer)*

One patient was struggling to find some kind of biochemical explanation, which she believed would be helpful in accepting the SSRI treatment.

> *For me it's quite difficult to take medication for this. That's because I don't know what exactly I'm using it for. Perhaps if they had told me there's a certain chemical that my body doesn't produce by itself, then I'd be okay with it. But no one told me that. People take cholesterol reducers because their cholesterol level is too high, but this is just so very different. (patient 3, discontinuer)*

Half of the patients did not express a need to find some kind of chemical or physical explanation as the root of their problems. Some patients could point out a life event, like a divorce or the death of a partner, as the provoking factor. Others realised that they had to identify the cause of their problems within their personality and personal life, and that they really needed to work on that.

Information on SSRI use

The patients reported being informed about several issues at the start of treatment.

> *The GP told me that the medication can take a little while to work, and what side effects might occur. He also said that I have to use it for at least six months, plus that I can't quit all of a sudden, but rather reduce the dose over time. (patient 11, continuer)*

Most patients reported being told that it would take several weeks before they felt a noticeable effect. A few were also aware that symptoms may even become worse during the first weeks, and one reported that suicidal ideation might occur. More than half of the patients said they had been informed about side effects which may occur immediately after the start of treatment. Half of the patients reported being aware that they should use the SSRI for a period of at least six months after remission of symptoms. Yet one patient was confident that four months was the absolute maximum allowed duration of treatment, and another stated that she could use the SSRI only when symptoms were worse, mostly for a couple of weeks at a time. In addition, half of the patients were cognisant of the need for tapering the SSRI when discontinuing treatment.

Patients judged the quality of information they received differently. Several patients seemed to be satisfied with the information received. They either relied on their GP and did not feel a need for further information, or were simply not interested in knowing everything about the medicine.

> *The doctor didn't discuss any side effects. That's what I had indicated, because when they tell you, then you'll probably get them. I don't ask any questions, I don't need to know everything. (patient 18, continuer)*

A few others were less pronounced in their judgement, as they reported not being able to retain all the information due to their condition.

I don't remember what the GP said. From the conversation I had with him I only remember how it made me feel at the time. (patient 12, continuer)

Several patients emphasised that it is important to be prepared for the possible occurrence of side effects.

I was told by the GP that in the beginning I might feel rushed. I'm glad I learned about that, because I did suffer from that in the beginning. So when that happened I knew it was part of the process and would soon pass. (patient 3, discontinuer)

Six of the patients were outspokenly negative about the information they received at the start. They felt that information on the burden of side effects, the reason for using the SSRI, alternatives of SSRI treatment, and the consequences of discontinuation, were addressed inadequately.

When I started with this medication I didn't receive any information whatsoever, not even about side effects. They did tell me in passing that it could take a while before I would notice the intended effect. The doctors should be much keener about this. It would be so easy to just give the main messages, and refer to the information leaflet for more information. When I asked my doctor whether this medication has any side effects, he just grabbed a big book and said "If you like I can read them for you". (patient 6, discontinuer)

Although most patients were aware of the occurrence of side effects, several reported that they found them almost overwhelmingly bothersome.

The doctor didn't really explain the medication. Then I started reading the information leaflet; I was shocked to read the side effects that were listed. I was quite troubled by it and actually wanted to quit. (patient 2, discontinuer)

Some patients found the information about SSRIs not being addictive confusing. They were aware of the occurrence of withdrawal symptoms after discontinuation, and considered this a feature of dependency.

The first time the GP said it's not addictive. I had reduced the dose over time, but yet from the way I was walking it seemed like I was drunk. I had a headache all the time. I believe it actually is addictive. The doctors better stop telling that story. (patient 16, continuer)

Finally, three of the patients reported that they were not informed about either receiving an SSRI or the reason for receiving it. They were shocked when reading in the information leaflet that SSRIs are indicated for depression and anxiety.

My GP had consulted the gynaecologist and said there appeared to be something wrong with my hormone balance. I trusted him. I didn't know then that it was an antidepressant until later when I read the information leaflet. If a doctor can't explain why you need it, then you won't accept the medication as easily either. (patient 3, discontinuer)

The majority of patients relied on the GP and the information leaflet for information. All but two patients mentioned that they had read the information

leaflet. Some patients mentioned that they received a personalised information letter from the pharmacy as well, which they appreciated. A few mentioned that the pharmacy pointed out an interaction between the SSRI and another drug the patient had used. Most patients mentioned that they did not receive any further verbal information at the pharmacy. Only a few patients were active in gathering information from other sources, such as the Internet.

Similarities and disparities between discontinuers and continuers during initiation

Considering the experiences and beliefs of discontinuers and continuers, some similarities and disparities were revealed. The impression gained was that there was no clear difference between both groups in the perceived severity of their symptoms before the initiation of treatment, and in patients' previous experience with antidepressants. Nevertheless, discontinuers and continuers appeared to be different in some aspects. First, the treatment decision making process seemed to work out differently. Continuers more often asked for SSRI treatment themselves, while some of the discontinuers even reported having had no communication with their GP at the moment of prescription. In addition, the discontinuers more often seemed to have a more negative attitude towards SSRI therapy than the continuers. Most of the discontinuers would rather have handled their problems without an SSRI, and expressed concerns about the potential negative effects of the drug. The discontinuers in particular found it difficult to have an emotional problem, were intensively searching for explanations, and often seemed to be unconvinced that treatment was necessary. The continuers seemed to be more positive towards SSRI therapy and expressed less negative feelings. They also seemed to be more convinced of the necessity of using an SSRI. In this context, the serotonin deficiency explanation was helpful for some of the continuers in accepting the treatment offer. Finally, there seemed to be a difference in the amount and quality of information received, and the need for further information. The continuers more often reported being informed about treatment issues, and most of them expressed no need for further information. The discontinuers, on the other hand, appeared to be less satisfied with the information received, and half of them were actively searching for further answers.

Execution of SSRI treatment

After patients have accepted the proposal of drug taking and treatment has been initiated, execution commences. The following domains emerged within this phase and are described below: side effects of treatment, effectiveness of treatment, communication and counselling during treatment, and social support.

Side effects of treatment

Directly after starting most patients noticed one or more side effects. Half of all patients were extremely bothered or felt threatened by these effects. Palpitations, tremors, stomach problems, diarrhoea, dizziness, nausea, and vivid and strange dreams were reported. Within one month most of these effects had disappeared.

> *The first four weeks were really difficult. You don't feel too great to start with, and on top of that these side effects. The stomach aches were the worst part. I couldn't keep any food down, just tea I was able to manage. I was shaking a lot, felt nervous and restless. I had the feeling there was so much I was supposed to be doing, but I didn't have the energy to get to it. (patient 12, continuer)*

Side effects reported later on during treatment concerned decreased libido, bruising, sweating, dry mouth, lethargy, and apathy. Six patients mentioned that they did not experience any side effects.

Thus, passing through the first weeks was rather difficult for most patients. The side effects occurred immediately, while no relief of symptoms was yet perceived. Although most patients were aware of the possible occurrence of side effects, some of them had not expected the effects to affect them or to be that bothersome. After the first month, most patients reported that the burden of side effects had reduced. However, two-thirds still perceived side effects that influenced their functioning in everyday life in a negative way.

> *I was rather apathetic. Temporarily perhaps that's a good thing, but not over a long period of time. I no longer had the energy to take any initiative; it seemed as if I lived in a bell jar. (patient7, discontinuer)*

Effectiveness of SSRI treatment

After having used the SSRI for between one and six weeks, most patients experienced an improvement of their situation. Patients mentioned feeling less stressed, emotional, or anxious, and panic attacks gradually reduced. Most patients reported having more energy to take part in everyday life and were able to be more social again. They tried to structure the day by going to work, sporting, or doing housekeeping activities.

> *I'm a lot less tense now, and more relaxed. I can take setbacks a lot better, and don't let things get to me as much. I enjoy moving around and started picking up basic things like making coffee. The household is back in operation. (patient 10, continuer)*

A few patients mentioned that the improved situation allowed them to work on themselves and the underlying problem.

> *I no longer have panic attacks, and I'm not as scared. I'm noticing that the negative feelings are diminishing. I am more open now to positive aspects, which helps me focus on my inner self. (patient 16, continuer)*

Others expressed the feeling of being themselves, and brain and body belonging together again.

> *It really felt like a miracle pill; instead of 100% lousy I felt 100% good. Now I'm back to being capable of living my normal life; my head and body feel connected again. (patient 8, discontinuer)*

Several patients reported a flattening of emotions as an effect of treatment as well. This was considered quite useful during the difficult initial period, but patients at the same time realised that this effect should not last too long.

> *Negative things don't affect me as much any more, and I actually sort of like that for now. In a while, perhaps, I like to return to being aware of what I actually feel. (12, continuer)*
>
> *My emotions in general are more subdued. Some things I don't care about any more; I've become more egocentric. (patient 10, continuer)*

Although most patients felt better and appreciated this new situation, not all of them felt cured. Some patients reported that they still were not sociable and able to participate in everyday life. Others felt that their situation was not yet stable and that they still had a long way to go.

> *My head feels calmer now, it's not churning thoughts as much any more. It doesn't feel as heavy, though it's not stable yet. I still have days of much doubt, of not being my true self. (patient 15, continuer)*

Two of the patients reported that they hardly experienced any positive effect during the two months of treatment.

> *I received a medication that didn't do anything; the situation got worse. I kept sliding down further and further. (patient 6, discontinuer)*

Patients differed in valuing the role of the SSRI in their improved situation. For some patients, the fact that they felt better by using the SSRI implied that they really needed it. The initial doubts about the necessity of using an SSRI disappeared. On the other hand, a few were rather sceptical about the effect of the SSRI. They doubted whether the fact that they felt better was due to the use of the SSRI or due to a natural process of recovery or taking part in other activities, like sport.

> *My disease is a so-called "self-finishing process". I feel better now, but I don't know if it's thanks to the medication or just because of time passing. If you don't take anything, you'll also get better. Perhaps I just told myself to stop with all this nonsense. I started biking again; that may have actually helped me more than the Efexor. (patient 6, discontinuer)*

Communication and counselling during treatment

All patients discussed the role of the GP. Most of them had an outspoken opinion about their interaction with the GP, being either rather positive or rather negative. More than half of the patients judged the GP's communication and counselling

during treatment as positive. They seemed to have every confidence in the GP, who sympathised with their problems. They felt they were treated with respect and were taken seriously.

> *My relationship with our GP is really good. He is always willing to listen to my side of the story. He understands my situation; I think that's important. (patient 16, continuer)*

Several patients mentioned that their GP asked them to keep in contact on a regular basis, starting with an initial visit after the first two weeks, which they appreciated. Six patients, however, judged the GP's communication and counselling as fairly negative. Some of them hardly had any contact with their GP during treatment. They felt the SSRI was too easily prescribed and said that repeat prescriptions were sometimes written without seeing the GP. Others did have contact with the GP during SSRI treatment but perceived the information and communication on its use as inadequate. One patient indicated that it was not an issue for him that GPs do not have all the information; however, they should communicate that their knowledge is limited, and admit that they have their uncertainties about treatment as well.

> *My previous doctors never really counselled me. They just wrote out a prescription, opened a drawer, and before I knew it I was back outside. My current doctor is willing to admit he doesn't know everything. He's just trying to get things started again. He explains everything, and I feel comfortable to discuss my doubts with him. (patient 6, discontinuer)*

Furthermore, some patients felt the GP did not take their concerns and experiences with the SSRI, such as side effects, seriously.

> *The first four weeks I felt really lousy: heart palpitations, perspiring often, ear drums closing, and headaches. It was as if I was having a heart attack. I called the doctor at least six times because I thought it wasn't normal. The doctor kept telling me that these were common side effects, that I had just had to bite the bullet. I thought that was quite limited. (patient 7, discontinuer)*

Even patients who were generally positive about the GP's counselling sometimes felt the side effects were not taken seriously.

> *I did tell my GP about the bruising, but he wasn't too concerned. It's not about craving for attention, or making up stories; it just worries me. (patient 10, continuer)*

More than half of the patients received a type of psychotherapy next to SSRI treatment, varying from counselling by a psychiatrist or social worker to group therapy sessions. A few of them, but not all, benefited from these therapies. None of the patients reported that the pharmacist had contributed to their counselling. Some mentioned that they received contradictory and confusing information from different healthcare professionals, i.e. their GP, psychiatrist, or social worker.

I've discussed the medication with my GP, a psychologist, and a psychiatrist. They each have a different opinion, that's annoying. I was always told to avoid alcohol when taking an antidepressant. Then the psychiatrist told me: sure, that's what we're saying, but in principle there's no such correlation. Another example: my GP had told me to start off by taking one whole pill each time, which caused a lot of side effects. Then later the psychiatrist explained that you should actually start off with just half a pill. Those type of things make you feel uncertain. (patient 7, discontinuer)

Social support

All patients reported having discussed SSRI use with their partner and children, if any. In general, patients perceived them as supportive. According to patients, some of the partners initially had their doubts about the necessity of using an SSRI. However, later on during treatment they changed their opinion once they noticed that their partner felt better and was able to function in everyday life again.

In the beginning my husband was wondering if I truly needed it. I felt I did need it; other people can't judge that for me. Later he admitted that he has a way of knowing what I feel, and said that I should take it when I think it's necessary. (patient 16, continuer)

Most patients did not feel the need to tell people other than their partner and children about the SSRI. They reported several reasons for not telling. A few saw no benefit in telling others, as they were convinced of the necessity of using the SSRI and would not be bothered by the opinions of others.

Some people probably think it's crazy that I'm taking this medication. Only my family knows, and my friend. I use it and it helps me, and I don't care what anyone else says. (patient 17, continuer)

A few did not tell others because they felt ashamed and were afraid of being stigmatised. If they did tell others, they often described the SSRI in vague terms, or as something just calming.

My family knows I use medication, but what for they don't know. I believe they think it's just some relaxation pills, nothing more. I'd rather not tell anyone. I'm afraid to get labelled mentally unsound, and not being able to get rid of it. When I get back to work I want to have all of my job's responsibilities; no special treatments because of what happened to me. (patient 12, continuer)

A few patients appeared to have no hesitations in telling others about using an SSRI. However, the responses received differed strongly, and were either supportive or critical.

My immediate friends and relatives encourage it. They're not prejudiced; they don't think taking something like this means you're crazy. (patient 13, continuer)

When I talk about it with other people they're often wondering if taking this kind of medication is a wise thing to do. You hear a lot of negative stories about these medicines. That's a shame because I'm sure there are people who benefit from it. (patient 7, discontinuer)

Some patients reported that their partners played a crucial role in the decision to either continue or discontinue the treatment.

My husband plays an important role in these decisions. After all, you're really in it together. He saw me getting worse so told me I should quickly restart taking these pills. (patient 8, discontinuer)

My wife thinks this medication is scary since it's affecting your brain. That doesn't bother me. The list of side effects on the information leaflet was quite shocking to her. So we talked about it, and then asked our GP if I could stop using it. I am doing okay now, but the deepest fears haven't gone away yet. (patient 1, discontinuer)

Similarities and disparities between discontinuers and continuers during execution

Considering the experiences and beliefs of discontinuers and continuers during execution, there appeared to be no clear difference regarding the perceived effectiveness and side effects of treatment. Although two discontinuers said they hardly perceived any positive effect, other discontinuers, as well as the continuers, evaluated the effectiveness as positive. There was a difference, however, in how both groups described their current situation. Most continuers, but only one discontinuer, reported that they did indeed feel better, but were not yet cured and stable. Regarding the severity of perceived side effects, there did not seem to be a clear difference between discontinuers and continuers either, though there might be a tendency for continuers to experience side effects more often. A great disparity did seem to exist between discontinuers and continuers in terms of the level of GP communication and counselling. All continuers evaluated the communication and counselling as rather positive, had every confidence in their GP, and felt they were treated with respect. Yet six out of nine discontinuers evaluated the communication and counselling as negative, felt they were not taken seriously, judged the information received as inadequate, or reported having had hardly any communication during treatment with their GP. Finally, there did not seem to be a difference between discontinuers and continuers regarding social support during treatment. In general, both groups indicated that they were reticent in telling others about their SSRI use. Partners and children appeared to be merely important in supporting patients during treatment for most patients.

Discontinuation of SSRI treatment

During execution of treatment, at a certain moment between two and four months of starting, the discontinuers came to discontinue SSRI use, while the continuers still continued SSRI taking. The following domains emerged within this phase and are described below: the moment of discontinuation, considerations for discontinuation and continuation, and the reasons for and consequences of discontinuation (for the discontinuers only).

Moment of discontinuation

During the first months of execution, most patients gradually started to feel better. Generally, the burden of side effects decreased, and symptoms faded. Although all patients had initiated treatment, it did not restrain many of them from reconsidering the necessity of drug taking, indicating that they had not really accepted treatment. All discontinuers and half of the continuers seemed to balance the pros and cons of SSRI use during the execution phase.

> *In my case the benefits outweigh the downsides, as far as I can tell. Obviously I'm worried about the bruising and the muscle aches; what does that mean about what's happening in your body? Perhaps if I knew more about that I would decide to quit. But I had thought long and hard on whether I should start with it, so you don't quit just like that. After all, my quality of life did improve (patient 10, continuer)*

Both discontinuers and continuers reported having considerations about whether to discontinue or continue SSRI use, but in the end the discontinuers were the ones who came to stop treatment. Eight of them seemed to be just eager to stop and were simply looking for a reason and a moment; it appeared that they did not intend to use the SSRI any longer than they actually did. For most of the discontinuers, the actual moment of discontinuation was incidentally chosen and seemed not to be induced by a certain event.

> *The weather was fine and I was doing okay. I was tired of being dependent on medication any longer, so I just quit. I thought I could do without; others also can. (patient 3, discontinuer)*

Five of them discontinued the SSRI on their own initiative without informing the GP, while four discontinued the SSRI on the advice of, or in consultation with, the GP.

For the continuers, the benefits clearly outweighed the unfavourable effects. Most continuers stated that they had not considered discontinuing the SSRI earlier than six months after starting use; they were relieved that they were able to function in everyday life again, and did not want to take the risk to stop treatment. They said they would wait for the GP to indicate the appropriate moment to stop.

> *I don't believe I could do without my medication yet. I'm still feeling too unstable. Once I can quit I will do so, but I'm afraid I'll slide back to my previous conditions.*

I update the GP on how I feel and leave the decision when to quit to him. After all, he's the expert. Me, I don't have any experience with this. (patient 11, continuer)

One of the continuers discussed the idea of stopping with the GP, but he convinced her to continue treatment for some time.

I don't want to take any pills if it's not absolutely necessary. I had called the doctor to start reducing the dose. I thought, if I don't speak up, a year from now I would still be taking these pills. But he thought it was too soon, so I'll continue for a little while longer, which is fine. (patient 15, continuer)

Considerations for discontinuation

Discontinuers and continuers reported the same type of considerations for discontinuation of treatment. Arguments considered mostly by the discontinuers included: considering SSRI use as unnatural (by 6); expressing the desire to handle their problems on their own strength without the help of an SSRI (by 5); because of the flattening of feelings (by 4); and for fear of dependency, either physical or psychological (by 3). Furthermore, four discontinuers reported the experience of side effects, and one the ineffectiveness of treatment, as considerations for discontinuation of treatment. Finally, four discontinuers reported the fact of feeling better as a reason to consider discontinuation. Three of them were not sure whether they felt better due to the SSRI itself, because of other actions they had taken, or as part of the natural process of recovery. They seemed not to be confident that they really needed the SSRI.

I felt much better, and was not sure whether this was due to the fact that I started dancing and sporting again, or due to the medicine. That's what I wanted to find out, and that's why I stopped taking the medicine. (patient 6, discontinuer)

The continuers reported the same type of considerations for discontinuation: rather handling the problems on one's own strength (by 3); fear of dependency (by 3); considering SSRI use as unnatural (by 2); flattening of feelings (by 2); and experienced side effects (by 1). However, feeling better was not considered a reason for discontinuation by the continuers; it was rather a reason to continue treatment. Moreover, half of the continuers did not report any consideration for discontinuation.

Considerations for continuation

The fear of handling problems without the resource of an SSRI, and of relapse into their old situation of distress, were the major arguments made by the continuers to continue treatment. In addition, several of them indicated that they did not yet feel stable. One of the continuers also reported fearing the occurrence of withdrawal symptoms when discontinuing SSRI treatment, due to a previous negative experience with discontinuation.

The discontinuers did not express any considerations for continuation, such as the fear of relapse into their old situation. They felt better, and seemed not to regard their situation as unstable. Six of them were confident that they would reconsider SSRI treatment if and when it might appear necessary.

I'd like to try quitting one more time. If I still get the symptoms back even after this third time, then I'll accept that I just have to take this pill. Then it would no longer bother me. (patient 8, discontinuer)

Actual reasons and consequences of discontinuation

The discontinuers indicated feeling better, bothersome side effects (such as flattening of emotions, nightmares, suicide feelings, sexual problems, and blurred vision), an epileptic attack, ongoing concerns about harmful effects on the brain, ineffectiveness, and pregnancy, as the actual reasons for discontinuation. One of the discontinuers said she used the SSRI always when she experienced symptoms, but discontinued treatment when her symptoms disappeared.

So far, four of the discontinuers still felt good after discontinuing treatment. They seemed to feel relieved that they had stopped taking the SSRI.

To me, quitting was a very positive experience. I did suffer from side effects, but with every day I felt I was becoming more "me". I felt a boost in energy and started picking up activities. I do worry about the depression returning, knowing that I quit too soon. However, I would never take an antidepressant again. The cure is worse than the disease! (patient 7, discontinuer)

However, four discontinuers experienced a relapse of symptoms after discontinuation. They now said they realised that they needed to use the SSRI for a longer period of time, and three of them had already restarted SSRI use. Although they had failed in their attempt to discontinue treatment, they were at least happy that they tried.

I just couldn't go on any longer. So I started again; I have arranged it all myself. I just know by now that it's better for me to take this medicine. (patient 3, discontinuer)

Similarities and disparities between discontinuers and continuers regarding discontinuation

To a certain degree, discontinuers and continuers seemed to have the same type of considerations to discontinue treatment. Considerations to continue treatment, however, seemed to be almost absent among the discontinuers. Most of the discontinuers did not seem to be convinced about the necessity of treatment, and just tried to stop. They would only reconsider SSRI treatment when it appeared necessary. Yet, discontinuing treatment seemed to be out of order for the continuers. Half of the continuers did not state any consideration to discontinue. The fact that

the continuers felt better was an incitement to continue treatment, while it often seemed to be the opposite for the discontinuers.

Discussion

Our findings provide insight into the experiences and beliefs of patients who recently started SSRI treatment, and identified two patterns leading to either discontinuation or continuation of treatment. The disparities between patients who decided to stop taking SSRIs and patients who continued seemed to reach far beyond the patients' health threat and the therapeutic effects of the drug. There was no clear difference between the discontinuers and continuers in the perceived severity of symptoms before initiation of treatment, or in the perceived effectiveness and severity of side effects. However, there were disparities regarding: the role of the GP in decision making and counselling; the information received; patients' perceived knowledge on SSRI use; and patients' attitude towards SSRIs and illness.

Discontinuers perceived the GP's role as limited, both during initiation and execution of treatment. They seemed to be less involved in decision making regarding SSRI treatment, and sometimes had the feeling that they were somewhat forced into using the SSRI. The discontinuers often appeared to have little confidence in their GP and felt they were not taken seriously. Counselling with the GP during treatment was limited. Most of the discontinuers were not satisfied with the information received, and felt they lacked knowledge on SSRI use. In addition, the discontinuers' attitudes towards the SSRI were rather negative from the beginning. They had ambivalent feelings about taking SSRIs, even when the SSRI had proven to be effective and the bothersome side effects decreased after some weeks of use. The discontinuers often seemed unconvinced of the necessity of using an SSRI. They appeared to have a strong desire to discontinue treatment, while they showed no fear of relapsing into their old situation. The continuers, on the other hand, were rather satisfied with their GP's role during initiation and execution. They fully trusted the GP's decision to start and continue SSRI treatment. The continuers' attitude towards SSRI therapy seemed to be predominantly positive, and they barely doubted the necessity of using an SSRI. The continuers hardly considered discontinuation during execution, as their fear of relapse dominated.

By approaching all patients from the participating pharmacies who had started SSRI treatment during a certain time period, we aimed to obtain a broad and representative sample. However, we do not know if the respondents differed

substantially from those who did not respond. Considering the relatively high number of patients in the study being unemployed or retired, some selection might have occurred; employed patients might have had fewer opportunities or time available to participate in the research. In spite of this, the respondents' accounts illustrate a wide range of experiences and beliefs of patients when evaluating their treatment. It is not very likely that patients who are employed or somewhat younger differ widely in the range of experiences, beliefs, concerns, and uncertainties. During the interview patients were asked to refer to the whole drug taking process, covering a period of some months. It is important to note that patients' memories may not have always been clear. Patients were probably inclined to justify the choices they made regarding starting, continuing, or discontinuing treatment, and to present themselves in what they perceive as a logical way.

We believe it is a strength of our study that we looked beyond quantitative studies mainly aimed at identifying which patients prematurely discontinue treatment. Numerous factors have been hypothesised to be predictors of discontinuation, but up to now patients' behaviour towards SSRI treatment remains less well understood (22-25). This study provides more insight into patients' experiences and views on treatment in the first months after starting, and explores why patients make certain decisions regarding medicine taking. In this context, it appeared relevant that we obtained findings not only from patients who were still taking SSRIs, but also from patients who had stopped taking the SSRI. Discontinuers and continuers showed great similarity in terms of the perceived impact of symptoms on their everyday lives, as well as the perceived effectiveness and side effects of treatment. Yet the groups showed important disparities in other domains, providing essential information about what needs to be taken into account, from the patients' perspective, when supporting them during use. It should be noted that assigning the patients as either a continuer or discontinuer is somewhat arbitrary as it is merely an observation of the treatment status at the moment of the interview. Some of the discontinuers were thinking of restarting, or had already restarted SSRI use, while continuers may have discontinued SSRI use shortly after the interview. We believe, however, that it does not detract from the two clear patterns that were found. The discontinuers made a reasoned decision to discontinue treatment, while most continuers hardly considered this. It appeared also advantageous to distinguish between the phases of drug taking – initiation, execution, and discontinuation – in order to identify the emerging domains and disparities. Some domains played a role in more than one phase, such as attitudes towards SSRI taking which may be modified in light of further experience with treatment during the execution phase. Yet the chronological exploration of the course of drug taking provides essential information on when patients experience difficulties, and whether and how these

can be addressed. Also unique in this study is the focus on the first months of treatment. Patients were able to tolerate the first difficult weeks of SSRI use; in these weeks, the burden of side effects is high, while recovery from symptoms is often not perceived. After two months, patients generally feel better as the bothersome side effects often decrease and symptoms remit. Nevertheless, in practice many patients stop treatment at this point, which is not in accordance with guidelines (14,26). Less is known about the specific experiences and beliefs of patients in this period, as up to now most qualitative studies have focussed on patients with a longer history of SSRI use, often more than one year (10,20,27-29). Two of these studies showed that long term SSRI users continued treatment for the time being, as they were afraid to live a life without SSRIs (20,29). These patients felt they were better safe than sorry. The discontinuers in our study, on the other hand, had a strong desire to discontinue SSRI treatment; they preferred to be sorry rather than safe. Although they initiated treatment and passed through the initial weeks, they had very ambivalent feelings and never really seemed to have accepted the SSRI. Other studies of long term users also showed patients discontinuing their antidepressant as an experiment to test the efficacy of the medicine and to discover whether the medicine is still needed (18,27). Feelings of psychological dependency on the antidepressant and denial of the disease, rather than side effects, were seen by the authors as the underlying reasons (18,27).
By focusing on experiences and beliefs leading to discontinuation, it was not our intention to suggest that the discontinuers should, at any costs, have continued SSRI treatment during the recommended period of six months (14,26). Discontinuation might be considered an informed decision about medicine taking. Unfortunately, we doubt whether this was the case for the discontinuers in our study, as they lacked information on use and appropriate counselling by their GP. Several discontinuers experienced a relapse of symptoms and had to restart SSRI use. Discontinuation of SSRI treatment under circumstances that appeared to be suboptimal seemed not to be the best option for patients.

In conclusion, we believe that our study provides essential information about the factors that need to be taken into account from a patient's perspective when starting SSRI treatment, and during the first months of use. Lack of shared decision making between patient and GP, limited counselling during treatment, lack of knowledge on use, and patients' negative attitude towards SSRI use and the disease itself, hampered the acceptance of the SSRI and brought on the decisional conflict to discontinue treatment during execution. Using medication is an active process that involves complex decision making and a chance to work through decisional conflicts (30). General practitioners and other healthcare professionals, like pharmacists, should be more supportive during the commencement and first

months of SSRI treatment by eliciting patients' considerations to either continue or discontinue treatment.

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3.3 Evaluation of patients' experiences with antidepressants reported by means of a medicine reporting system

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Abstract

Introduction

Reporting systems have shown to be a useful tool in collecting experiences and identifying issues related to the daily use of medicines. The aim of this study was to assess experiences related to antidepressant use reported to an internet-based medicine reporting system and to compare the nature of side effects reported by patients with those reported by healthcare professionals (HCPs).

Methods

All reports submitted from May 2004 to May 2005 to an internet-based medicine reporting system in the Netherlands related to the use of antidepressants were analysed. Spontaneous reports of adverse drug reactions on antidepressants from HCPs received by the Netherlands Pharmacovigilance Centre Lareb from May 2004 to May 2005 were included for comparison.

Results

Of the 2232 individuals who submitted a report to the internet-based medicine reporting system, 258 submitted a report on antidepressants. Of these, 92 individuals (36%) reported on effectiveness, 40 (16%) of whom reported on ineffectiveness, and 217 (84%) submitted a report on side effects, with 202 (78%) reporting a total of 630 side effects that were experienced as negative. Fourteen individuals (5%) reported a practical issue and four reporters (2%) reported a reimbursement issue. Of all 630 side effects reported, 48% resulted in the patient discontinuing the antidepressant therapy; of these 29% did not inform their HCP. Of all the side effects reported, 52% were perceived as "very negative". In comparison to the side effects reported by HCPs, patients more often reported apathy, excessive sweating, ineffectiveness, somnolence, insomnia, sexual problems and weight increase.

Conclusion

Patients report the ineffectiveness and side effects of antidepressant therapy as negative and leading to discontinuation of the therapy. Patients and HCPs differ in the nature of the reported side effects. Patient experiences should be included in the evaluation of antidepressant treatment in clinical practice.

Introduction

Non-adherence to prescribed medication regimens is a persistent problem in the treatment of depression with antidepressants. Premature discontinuation, dosing lapses and partial non-adherence often occur (1-3). The illness itself as well as physician-, patient- and treatment-related factors have been suggested to contribute to antidepressant non-adherence, but the ability of healthcare professionals (HCPs) to predict who discontinues medication remains poor (4-6). Earlier studies provide scant information on how patients in clinical practice perceive their treatment with antidepressants, thus insight and an understanding of the patients' perspective on non-adherence and discontinuation are limited. Side effects and ineffectiveness are the major reasons cited for the discontinuation of antidepressant therapy (7,8). However, the information available on side effects is mostly based on controlled clinical trials, which standardly do not evaluate how bothersome side effects are to the individual patient. Moreover, both the side effects and the effectiveness of the antidepressant therapy observed in clinical trials may not reflect the experiences of the patients in real world settings. Many interventions have been developed to improve adherence to antidepressants, but to date these have failed to demonstrate a clear benefit (9,10). Treatment non-adherence remains one of the least understood health-related behaviours. Information received directly from the patient may improve our understanding of the relative importance of antidepressant treatment issues and, consequently, help to explain patients' behaviour towards antidepressant use.

Reporting systems have shown to be a useful tool in collecting experiences and identifying issues related to the daily use of medicines (11). In 2004, an internet-based medicine reporting system was established in the Netherlands where users of medicines are able to report all types of experiences with medicines – side effects as well as experiences with effectiveness and practical and reimbursement issues. We extracted data from this medicine reporting system in order to (1) assess the type of experiences related to antidepressant use reported by patients, (2) assess the relevance of these experiences and (3) compare the nature of the suspected side effects reported by patients with those reported by HCPs.

Methods

Setting

Reports were obtained from an internet-based medicine reporting system launched on 11 May 2004 in the Netherlands. This reporting system was initiated by DGV, The Dutch Institute for the Proper Use of Medicine, the Science Shop

for Medicines and patient and consumer organisations. Individuals are able to report their experiences with medicines anonymously by completing a report form downloaded by accessing a website (http://www.meldpuntmedicijnen.nl). Users of the medicine themselves as well as their relatives, acquaintances or (professional) carers, can report an experience. All reports submitted between 11 May 2004 and 13 May 2005 related to the use of antidepressants were reviewed for the clarity and completeness of the description of the experience and checked for multiple reports from the same IP-address. One duplicate report had to be excluded. All other reports were included in the study. The data were stored in an Access database.

Report form

The report form contained items which requested information on age, gender, type of medicine used, nature of the experience, a description of the experience and the relevance of the experience. Individuals filling in the report had to indicate whether the experience was related to either effectiveness, a side effect, a practical issue (e.g. difficulties with swallowing tablets) or a reimbursement issue. More than one experience related to the same drug could be submitted. Experiences related to effectiveness had to be further specified by the individual by selecting one of the following categories: ineffectiveness, a positive effect or a different type of effect (e.g. drug interactions). Experiences related to side effects had to be further specified by selecting one of the following categories: negative side effects, positive side effects (e.g. less side effects as compared with previous medication) or the absence of side effects. Relevance of the experience was assessed by asking the individual filling in the report to indicate both the impact of the experience on a 5-point scale (ranging from very negative to very positive) and whether the experience caused a change in antidepressant use. To specify the change in antidepressant use, those reporting had to select one of the following categories: discontinuation, switching to other treatment, adjustment of dosage or administration, any other action taken or no action taken. In the case of discontinuation of the antidepressant, the report also asked whether the HCP has been informed.

Side effects

All reported side effects (including experiences on ineffectiveness) were coded by one of the authors (SvdW) and checked by a second author (EvG), using preferred terms of the World Health Organisation Adverse Reaction Terminology (WHO-ART) (12). Preferred terms were combined into groups of similar side effects. Spontaneous reports of adverse drug reactions on antidepressants received from HCPs from May 2004 to May 2005 were included for comparison. These reports were received by the Netherlands Pharmacovigilance Centre Lareb either on

paper forms or electronically via http://www.lareb.nl. Coding and assessment were carried out by qualified assessors from Lareb (13).

Data analysis

The relevance of the side effects was assessed by comparing the impact of the (grouped) side effects as a proportion of the side effects that were perceived as "very negative". Relevance was also assessed by comparing the proportion of the side effects that caused discontinuation of initial antidepressant use, including the categories "discontinuation" and "switching to other treatment". The impact and discontinuation proportions of the different groups of side effects were compared using the Chi-square test.
For the comparison between patients and HCPs, the groups of side effects were compared and expressed as an odds ratio (OR) and 95% confidence interval (CI). The 15 most frequently reported (groups of) side effects by patients as well as the 15 most frequently reported (groups of) side effects by HCPs were included in the analysis.

Results

Characteristics

In total 2232 individuals submitted a report to the medicine reporting system during the study period, of whom 258 (12%) submitted a report on antidepressants. Of these 258 individuals, 248 (96%) reported for themselves and ten reported for a relative or acquaintance.
The mean (±SD) age of the of the antidepressant users was 42.8 (±13.5) years and 72% were female. The majority of those reporting on antidepressants (63%) were reporting on a serotonin-reuptake inhibitor (SSRI); 12% were reporting on a tricyclic antidepressant (TCA) and 25% on another type of antidepressant. The antidepressants most frequently reported on were paroxetine (35% of total), venlafaxine (15%), citalopram (10%) and mirtazapine (8%). The use of a benzodiazepine as a concomitant drug was reported by 19% of those reporting on antidepressant use.

Nature of experiences

The 258 individuals reporting on antidepressant use described 327 experiences. Table 1 shows the nature of the experiences described. Ninety-two individuals (36%) described an experience with effectiveness, of whom 40 (16%) described an experience with ineffectiveness. Four individuals claimed generic substitution as the reason for ineffectiveness, and 45 (17%) reported a positive experience with the

Table 1 Nature of the reported experiences related to antidepressant use reported to a medicine reporting system (http://www.meldpuntmedicijnen.nl) [a]

Issue	Proportion of total number of individuals (n=258) reporting on antidepressant use	Nature of issue	Proportion individuals reporting on a specific issue
Effectiveness	36% (n=92)	Ineffectiveness	16% (n=40)
		Positive effect	17% (n=45)
		Other	3% (n=7)
Side effects	84% (n=217)	Negative side effect	78% (n=202)
		Positive side effect	1% (n=3)
		Absence of side effect	5% n=12)
Practical issues	5% (n=14)		
Reimbursement and availability issues	2% (n=4)		

a A total of 258 reporters submitted 327 experiences. The reported experiences are expressed as a percentage of the total number of individuals submitting reports

effectiveness of an antidepressant. "Other type of effects" in terms of effectiveness that were submitted by seven (3%) individuals included experiences on suspected drug interactions.

In total, 217 of the 258 individuals (84%) reporting on antidepressant use submitted a report on side effects. Of these, 202 (78%) described a total of 630 side effects that were experienced as negative. The number of reported side effects ranged from 1 to 11 per reporter experiencing a negative side effect. Twelve individuals (5%) reported that they had not experienced any side effect at all, and three (1%) submitted a positive experience with side effects, reporting that their current antidepressant therapy caused fewer side effects than their previous medication.

Fourteen individuals (5%) reported a practical issue (such as problems with swallowing tablets or bad taste), and four reporters (2%) reported a reimbursement or availability issue (receiving treatment for a relative short duration).

Box 1 shows a number of the reported experiences.

Relevance of side effects

Table 2 shows the relevance, impact and discontinuation rates of the most frequently reported side effects. Of all side effects, 48% resulted in discontinuation of the initial antidepressant therapy. The proportion of side effects that caused discontinuation of the initial antidepressant did not differ significantly between the different side effects. Of those individuals who simultaneously reported an experience on side effects and one on ineffectiveness, 59% (17/29) reported that their experience resulted in discontinuation of the initial antidepressant therapy. Of all individuals who reported discontinuation of therapy, 29% did not inform their HCP.

Box 1: Examples of experiences reported to the patient reporting system

Effectiveness and side effects
The medicine works well; its advantage is that it doesn't feel like a 'blanket' is draped over you as with medicines such as oxazepam. By the way, the less expensive substitute paroxetine didn't work for me. The use of Seroxat has the major drawback that it is physically addictive! After taking it for a year and a half, tapering off was next to impossible and certainly not in the way it is stated in the information leaflet. During use I experienced the following side-effects: itchiness, mucous build-up in the throat, incomplete voiding, sensitivity to light, blurred vision, increased heart-rate, concentration disturbances, sweating, nausea, constipation.
Ineffectiveness and side effects
The medicine doesn't work and the side effects are worse than the ailment. Furthermore some side effects aren't even mentioned in the information leaflet, such as permanent damage to teeth. Side effects are: being unable to concentrate, a blurring of emotions, cavities – dentists can tell by the teeth if a person is taking SSRIs, tremors (it's as if I'm an alcoholic), insomnia and lack of deep-sleep, constant headaches (in the back of the head), a continuous nagging pain in all limbs. Like having a hangover – feeling apathetic.
Side effects
I tapered off the medicine in one month and had many side effects: rapid mood changes, 'flashes' in the head, sharpening of senses – seeing and hearing, anxiety, dizziness, nausea, headaches, diarrhoea, panic attacks, heart palpitations, fainting. I did not experience these side effects until I stopped using the medicine.
Practical issues
The tablet doesn't have a smooth layer, causing it to get stuck in the oesophagus quite frequently. This, in turn, leads to a foul taste in the mouth, an unpleasant sensation, retching, sometimes only resolved by vomiting. This is really disturbing to me and I don't understand why the manufacturer doesn't make the effort to add a smooth layer around the tablets.
Reimbursement and availability issues
It's a real burden to me that this medicine, which I have to take permanently, is always prescribed for just thirty days (without a refill prescription). I always have to get a new prescription, which is completely unnecessary, especially if you take into account the costs of prescribing.

Table 2 Relevance of the most frequently reported side effects related to antidepressant use

Side effect	Number of reported experiences (n)	Impact (% perceived as "very negative")	Discontinuation of antidepressant use (%)
Sleep disorder	68	47	50
Somnolence, drowsiness, fatigue	39	51	59
Insomnia, sleeplessness	29	41	38
Weight increase	48	46	56
Sexual problems	43	44	33
Discontinuation symptoms	40	43	50
Ineffectiveness	40	35	53
Apathy	28	46	54
Excessive sweating	23	43	39
Nausea, gagging	23	39	30
Dizziness, fainting	23	65	35
Headache	22	68	50
Dry mouth	18	50	61
Suicidal attempt, thought or tendency [a]	9	78	78

a Suicidal attempts, thoughts or tendency is also included, although the number of reported experiences was less than 15

Of all side effects, 52% were perceived as "very negative". The impact of the side effects differed almost significantly between the groups of side effects (p=0.052), with headache, dizziness and fainting perceived as most negative.

Table 3 Reported side effects on antidepressants by patients compared with reported side effects on antidepressants by healthcare professionals (HCPs)

Side effect	Number of reported side effects by patients	Percentage of total number of side effects (n=670)	Number of reported side effects by HCPs	Percentage of total number of side effects (n=471)	Odds ratio (95% CI) [a]
Top 15 most frequently reported side effects by patients					
Weight increase	48	7.2	6	1.3	5.98 (2.54-14.09)
Sexual problems	43	6.4	6	1.3	5.31 (2.24-12.59)
Discontinuation symptoms	40	6.0	3	0.6	14.14 (4.35-45.93)
Ineffectiveness	40	6.0	3	0.6	14.14 (4.35-45.93)
Somnolence, drowsiness, fatigue	39	5.8	8	1.7	3.58 (1.66-7.73)
Insomnia, sleeplessness	29	4.3	4	0.8	5.28 (1.84-15.13)
Apathy	28	4.2	0	0	-
Excessive sweating	23	3.4	0	0	-
Nausea, gagging [b]	23	3.4	8	1.7	2.05 (0.91-4.64)
Dizziness, fainting [b]	23	3.4	8	1.7	2.05 (0.91-4.64)
Headache [b]	22	3.3	11	2.3	1.42 (0.68-2.96)
Dry mouth	18	2.7	3	0.6	4.31 (1.26-14.71)
Abdominal pain	14	2.1	3	0.6	3.33 (0.95-11.65)
Anxiety	13	1.9	2	0.4	4.64 (1.04-20.66)
Depressed mood	11	1.6	3	0.6	2.60 (0.72-9.39)
Top 15 most frequently reported side effects by HCPs					
Rash, urticaria and pruritis	3	0.4	23	4.9	0.09 (0.03-0.29)
Laboratory abnormalities	0	0	22	4.7	-
Muscle and joint complaints	3	0.4	20	4.2	0.10 (0.03-0.34)
Congenital disorders	0	0	15	3.2	-
Eye and vision disorders	6	0.9	15	3.2	0.27 (0.11-0.71)
Paraesthesia	8	1.2	12	2.5	0.46 (0.19-1.14)
Headache [b]	22	3.3	11	2.3	1.42 (0.68-2.96)
Extrapyramidal disorders, Parkinsonism	1	0.1	10	2.1	0.07 (0.01-0.54)
Menstrual disorders, vaginal bleedings	3	0.4	10	2.1	0.21 (0.06-0.76)
Heart rhythm problems	7	1.0	10	2.1	0.49 (0.18-1.29)
Convulsions, epilepsy	0	0	9	1.9	-
Drug substitution problems	7	1.0	8	1.7	0.61 (0.22-1.70)
Serotonin syndrome	0	0	8	1.7	-
Nausea, gagging [b]	23	3.4	8	1.7	2.06 (0.91-4.64)
Dizziness, fainting [b]	23	3.4	8	1.7	2.06 (0.91-4.64)

a OR>1: Patients were more likely to report the side effect than the HCPs; OR<1: HCPs were more likely to report the side effect than the patients. 95% CI, 95% confidence interval
b Side effects that appear in both the patients' and HCPs' list

Side effects compared between patients and HCPs

Table 3 presents those side effects most frequently reported by patients and HCPs. Patients and HCPs differed in the nature of reported side effects. Compared with HCPs, patients reported significantly more events such as apathy, excessive sweating, ineffectiveness, discontinuation symptoms, somnolence, insomnia, sexual problems

and weight increase. HCPs reported significantly more rash, pruritis, laboratory abnormalities, muscle and joint complaints, congenital disorders, eye disorders, extrapyramidal disorders and menstrual disorders than patients.

Discussion

Both side effects and a lack of effectiveness appear to be important treatment issues for patients who reported on antidepressants in our study. Most of the individuals reporting on antidepressant use described one or more side effects, of which the most frequent were weight increase, sexual problems, somnolence, insomnia and apathy. Ineffectiveness was also reported by a considerable number of individuals. Ineffectiveness is not often reported in literature as an adverse effect of treatment (14). However, our study reveals that it is a relevant issue for patients during antidepressant therapy. The fact that side effects tend to occur before the therapeutic effect of the antidepressant is perceived may play an important part in explaining early discontinuation of the therapy. Ineffectiveness should therefore receive attention from HCPs in order to prevent early discontinuation of antidepressants.
One of the unique features of this medicine reporting system is the possibility to gather information on the relevance of the experiences – that is the impact of the experience and the change in initial treatment. Overall, half of the experiences were perceived as very negative. Experience of one or more bothersome side effects means an individual is threefold more likely to stop taking antidepressants (7). Our results show that one half of the side effects resulted in discontinuation of the initial antidepressant therapy. Moreover, of all those individuals who reported discontinuation of therapy, 29% did not even inform their HCP. This supports the concept that this medicine reporting system provides data of which HCPs are often not aware, but which are of crucial importance to any understanding of patients' behaviour related to the use of antidepressants.

Patients and HCPs differed in the nature of the side effects reported. Patients were found to report more frequently those events which may be less tangible and visible to HCPs, such as sleeping problems and apathy. In addition, HCPs may consider symptoms reported by patients with psychiatric disorders as a symptom of the disease rather than as one related to the medication. Other notable differences between patients and HCPs in terms of the frequency of reported side effects were those of weight increase, sexual problems, discontinuation symptoms and excessive sweating. The differences in the nature of the reported side effects show that patients and HCPs differ in which type of side effects can be considered to be bothersome and/or relevant to report. The burden of side effects is clearly underestimated by

HCPs (15). Although HCPs are knowledgeable on the side effects related to SSRI use, they underestimate the frequency of these side effects and how bothersome they are to patients (16). In addition, HCPs may be reticent in reporting a side effect to a reporting system. More than patients, HCPs evaluate the side effect reported by the patient according to perceived relevance and causality related to the medication. Side effects which are considered by the HCP as well-known or not related to the medication consequently get lost to the healthcare system (17). Patient reporting is not yet widely accepted, and the number of systems collecting experiences from patients is still limited. In the UK, the Prescription-Event Monitoring (PEM) system seeks to identify adverse events recorded following the use of newly marketed drugs selected for monitoring on the first 20,000-50,000 patients given the new drug (18). Since the middle of 2003, the Danish Medicines Agency and the Netherlands Pharmacovigilance Centre Lareb also accept reports on adverse drug reactions from patients (19). In Sweden, the KILEN Consumer Institute for Medicines and Health started a consumer database in 1997 that collects experiences related mainly to dependence and side effects of benzodiazepine and antidepressant use (19). However, these systems focus only on adverse events, while other aspects of medicine use, including experiences on ineffectiveness, practical and reimbursement issues, have also been shown to be relevant to patients.

A limitation of this internet-based reporting system is that the reporters are anonymous and, therefore, further contact and feedback are not possible. Consequently, a thorough assessment of causality between the side effect and the antidepressant was not always possible. The Netherlands Pharmacovigilance Centre Lareb, on the other hand, whose primary aim is the early detection of new adverse drug reactions, has the facilities to request further medical information by contacting the patient and/or his/her HCP (20). However, we believe this does not detract from our conclusion. The individuals reporting through the internet-based reporting system proved to be capable of providing clear descriptions of their experiences and of balancing the benefits and burden of treatment. The patient experiences provide important information on how patients in clinical practice perceive treatment with antidepressants. Such patients experience sleep disorders, weight increase, sexual problems, apathy and ineffectiveness as events which have a negative impact and which frequently lead to discontinuation of the antidepressant therapy. Because adherence decisions are mostly a rational balance of perceived benefits versus burden (21), an assessment of patient experiences may improve the understanding of patients' behaviour towards antidepressant use. This information can be used in the development of more targeted adherence-enhancing strategies that may lead to optimisation of antidepressant treatment from the perspective of both HCPs and patients.

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4 Discontinuation of antidepressant therapy

4.1 Patients' concerns about and problems experienced with discontinuation of antidepressants

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Abstract

Introduction

Clinical trials and epidemiological studies have shown that premature discontinuation is a major problem during antidepressant therapy. Unfortunately, there is little information on how patients perceive treatment with antidepressants in clinical practice, and it is unclear whether patients perceive discontinuation as a problem. The objective of this study is to assess whether concerns and problems experienced with drug discontinuation occur more frequently in patients using antidepressants than in patients using benzodiazepines, antipsychotics or non-psychiatric medication.

Methods

All calls to a national telephone medicines information service received between 1990 and 2004 were examined using retrospective examination. Calls about discontinuation were identified and classified either as a general question about discontinuation, or as a problem experienced with discontinuation. These calls were grouped into the following main classes: antidepressants, antipsychotics, benzodiazepines or non-psychiatric medicines.

Results

Of all 39,786 registered phone calls, 6159 (15.5%) related to antidepressants, 1658 (4.2%) to antipsychotics and 3916 (9.8%) to benzodiazepines. Patients calling about antidepressants called about discontinuation three times as often (odds ratio (OR) 2.8; 95% confidence interval (CI) 2.6-3.0), and reported a problem with discontinuation five times more often (OR 5.4; 95% CI 4.6-6.3), compared to patients who called about non-psychiatric medicines. The proportion of questions about discontinuation and problems experienced with discontinuation was also higher in patients calling about benzodiazepines and antipsychotics compared to patients calling about non-psychiatric medication.

Conclusion

Patients perceive discontinuation of antidepressants, as well as discontinuation of antipsychotics and benzodiazepines, as a problem. Discontinuation seems a general problem for all psychiatric medicines, and needs more attention in the communication between patients and healthcare providers.

Introduction

Clinical guidelines recommend that patients treated with antidepressants should continue their therapy for at least six months after remission of symptoms (1). However, clinical trials and epidemiological studies have shown that premature discontinuation is a major problem during antidepressant therapy. About one-third of the patients abruptly discontinue antidepressant treatment within the first two months, and as many as half of patients discontinue treatment within the first six months (2, 3). Dosing lapses and partial non-adherence also often occur (4, 5). In addition, one in five patients who stop therapy, abruptly discontinue their antidepressant instead of tapering, which increases the risk of unwanted withdrawal symptoms (6).

Unfortunately, there is little information on how patients perceive treatment with antidepressants in clinical practice, and it is unclear whether patients perceive discontinuation as a problem. Information received directly from the patient may improve the understanding of patients' behaviour towards discontinuation of antidepressant use. The analysis of calls received by a specialist helpline confirmed the high prevalence of discontinuation symptoms with antidepressants (7). A national telephone medicines information service in the Netherlands has been shown to be a useful tool in identifying problems related to the daily use of medicines (8). We used calls from this telephone information service with the objective to assess whether concerns and problems experienced with drug discontinuation occur more frequently in patients using antidepressants than in patients using benzodiazepines, antipsychotics or non-psychiatric medication.

Methods

In 1990 a national telephone medicines information service was started by consumer organisations and the Royal Dutch Association for the Advancement of Pharmacy, supported by the Dutch Ministry of Health. Through this service, patients or their carers can consult a pharmacist anonymously. Pharmacists are requested to complete a standard form for each call, registering the sex and age of the caller, drug names involved and a short description of the call itself. The forms are stored in a database. All calls registered between the beginning of the information service in 1990 and November 2004 were included in the study. Ethical approval was not required for this study.

Calls about discontinuation were identified with a free-text search using keywords (or parts thereof) for discontinuation (e.g. 'tapering', 'reduce', 'discontinuation symptoms', 'withdrawal', 'stopping'). These calls were reviewed by two of the

authors (KvG and MB) independently, in order to classify the call as either a general question about discontinuation, or a problem experienced with discontinuation. In case of disagreement about the classification, the call was assessed by four of the authors to reach agreement. Questions about discontinuation include questions on whether, when and how to discontinue the medicine, and what to expect during discontinuation of the medicine. Problems experienced with discontinuation include the following: the occurrence of discontinuation symptoms following dose reduction or abrupt discontinuation, or recurrence of previous symptoms of the disease. All calls were grouped into the following main classes: antidepressants, antipsychotics, benzodiazepines, or non-psychiatric medicines. The total number of calls about antidepressants, antipsychotics and benzodiazepines was related to the mean number of users during the study period in the Netherlands, obtained through the Drug Information System of the Health Insurance Board (www.gipdatabank.nl). Antipsychotics and benzodiazepines were included to assess whether discontinuation is a specific problem for antidepressants or a general problem for all psychiatric medicines. The calls about discontinuation and the problems with discontinuation were compared between antidepressants, antipsychotics, benzodiazepines and non-psychiatric medicines expressed as an odds ratio (OR) and 95% confidence interval (CI). Chi-square test was used to compare proportions of calls and problems with discontinuation between antipsychotics, benzodiazepines and antidepressants. Antidepressants were classified further into tricyclic antidepressants (TCAs), serotonin-reuptake inhibitors (SSRIs) and other antidepressants. The calls about discontinuation and the problems with discontinuation were compared between TCAs, SSRIs and other antidepressants expressed as an OR and 95% CI. Chi-square test was used to compare the proportions of calls and problems with discontinuation between TCAs and SSRIs, male and female, and age categories.

Results

Between 1990 and November 2004, the national telephone service registered 39,786 phone calls. Of these, 6159 (15.5%) calls related to antidepressants. Of all calls about antidepressants, most callers were women (72%) and were aged between 21 and 40 years (55%) and 41 and 60 years (43%). Table 1 shows the total number of calls about discontinuation and the number of problems experienced with discontinuation for the different classes of medicines. Related to the total number of users during the study period in the Netherlands, antidepressant and antipsychotic users called four times as often to the telephone service as did benzodiazepine users. Relatively, there were three times as many calls about discontinuation of antidepressants and

Table 1 Calls to a national telephone information service between 1990 and 2004 related to drug discontinuation

	Total number of calls	Calls about discontinuation			Problems with discontinuation		
		n	% of total	OR (95% CI)	n	% of total	OR (95% CI)
Non-psychiatric medicines	28053	1982	7.1	reference	292	1.0	reference
Antidepressants	6159	1072	17.4	2.77 (2.56-3.00)	329	5.3	5.37 (4.57-6.30)
Antipsychotics	1658	255	15.4	2.39 (1.93-2.46)	68	4.1	4.07 (3.11-5.32)
Benzodiazepines	3916	755	19.3	3.14 (2.87-3.44)	239	6.1	6.18 (5.19-7.36)
Classes of antidepressants [a]							
TCA	1315	273	20.8	reference	77	5.9	reference
SSRI	3612	606	16.8	0.77 (0.66-0.90)	189	5.2	0.89 (0.68-1.17)
other antidepressants	1038	170	16.4	0.75 (0.60-0.92)	60	5.8	0.99 (0.70-1.40)

a Totals do not add up to 6159 due to unknown type of antidepressant used

five times more problems experienced with discontinuation of antidepressants, compared to calls about non-psychiatric medicines. The proportion of calls about discontinuation and problems experienced with discontinuation was also higher in patients calling about benzodiazepines and antipsychotics compared to patients calling about non-psychiatric medication. Patients calling about antidepressants called more often about discontinuation ($p=0.05$) and experienced more problems with discontinuation ($p=0.04$) than patients calling about antipsychotics. Compared to patients calling about benzodiazepines, the antidepressant users less often called about discontinuation ($p=0.02$), but did not differ in the proportion of problems experienced with discontinuation ($p=0.11$).

Regarding the two major classes of antidepressants, patients taking TCAs more often called about discontinuation compared to patients taking SSRIs ($p=0.001$), but did not differ in the number of problems experienced with discontinuation ($p=0.39$). The relative number of calls about and problems with discontinuation remained constant through time for the major classes of antidepressants as well as the individual antidepressants.

Compared to men, women more often called about discontinuation (18.9% versus 14.5%; $p<0.001$) and experienced more problems with discontinuation (5.8% versus 4.4%; $p=0.03$). There was no difference in the number of calls about discontinuation ($p=0.09$) and the number of problems experienced with discontinuation ($p=0.80$) for the different age categories.

Discussion

Patients calling about antidepressants called about discontinuation three times as often, and reported a problem with discontinuation five times more often, compared to patients who called about non-psychiatric medicines. A higher proportion of concerns about discontinuation and problems experienced with discontinuation was also seen in patients calling about antipsychotics and benzodiazepines compared to patients calling about non-psychiatric medication. Our findings show that patients perceive discontinuation of antidepressants, as well as discontinuation of antipsychotics and benzodiazepines, as a problem. Long-term use of these psychiatric medicines, together with the high rates and burden of adverse effects, is likely to be an important factor in the explanation of this general issue of discontinuation. In addition, most patients consider psychiatric medicines to be addictive, and want to take these medicines as short as possible (9,10). Moreover, most psychiatric medicines need to be tapered, which patients are often not aware of (6).

The strength of our study is that we received daily life experiences direct from patients. Information from clinical trials may not reflect experiences of patients in the real-world setting, and automated prescription data as used in epidemiological studies may not provide the insight needed to understand patients' behaviour. Moreover, patient experiences provide information of which doctors and other healthcare providers may not be aware, because patients who have stopped the medicine are often not under the direct care of a doctor, and a considerable number of patients do not inform their doctor about stopping the medicine (11,12). The use of calls from a telephone medicine information service also has its limitations. First, the nature of the illness may have introduced a response bias. Patients taking psychiatric medicines may be more likely to contact an information service line than patients taking non-psychiatric medication. Second, the calls represent only a small proportion of all medicine users, which means that the results may not be representative for all users. On the other hand, in this way only issues that are considered relevant and important by medicine users are revealed. In addition, we had no absolute evidence for the appropriate assessment of a problem in all cases, assessed as either the occurrence of discontinuation symptoms or recurrence of symptoms. Although our procedure required confirmation of assessment of the call by the other authors, a thorough assessment was not always possible. Nevertheless, these limitations do not undermine our conclusion. Insight in the issue of discontinuation of medicines can be improved by getting information directly from the patient. Discontinuation seems a general problem for all psychiatric medicines, and needs more attention in the communication between patients and healthcare providers (13).

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4.2 Discontinuation symptoms in users of selective serotonin-reuptake inhibitors in clinical practice: tapering versus abrupt discontinuation

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Abstract

Introduction

Tapering of selective serotonin-reuptake inhibitor (SSRI) therapy, as opposed to abrupt discontinuation, has been recommended by several guidelines and in literature in order to diminish the occurrence of discontinuation symptoms. However, the evidence of a favourable effect of tapering is limited, and it is unclear how patients discontinue SSRIs in daily life. The aim of this study was to examine the way in which patients discontinue SSRI therapy in clinical practice and to compare the effect of tapering with that of abrupt discontinuation on the occurrence of discontinuation symptoms.

Methods

Patients (n=74) who recently discontinued SSRI therapy completed a questionnaire containing questions about discontinuation symptoms (DESS events), the prescribed SSRI, reasons for discontinuation, way of discontinuation, knowledge of discontinuation symptoms, impact on daily life and patient counselling and education. The number of DESS events was compared among groups (abrupt discontinuation versus tapering; age; male versus female; paroxetine versus other SSRIs; knowledge of discontinuation symptoms at start of therapy versus lack of knowledge).

Results

A total of 66 patients were eligible for analysis. Of all patients ending SSRI therapy, 21% abruptly discontinued therapy. There was a significant difference in the number of DESS events between abrupt discontinuation and tapering of SSRI therapy (12.0 versus 5.9). There was also a tendency for an adverse effect of lack of knowledge of discontinuation symptoms at the start of therapy on the number of DESS events (8.9 versus 5.5).

Conclusion

One in five patients abruptly discontinued their SSRI therapy in clinical practice. Abrupt discontinuation caused a larger increase in the number of discontinuation symptoms than tapering. We therefore advise tapering SSRI therapy in clinical practice to prevent unnecessary adverse effects of discontinuation.

Introduction

In about one-third of the patients who stop therapy with selective serotonin-reuptake inhibitors (SSRIs) discontinuation symptoms occur, which can be bothersome, have an adverse effect on patients' quality of life and may lead to unnecessary renewed antidepressant use (1,2). In some patients, these discontinuation symptoms can even cause considerable morbidity, can be misdiagnosed leading to inappropriate treatment, and can adversely affect future antidepressant compliance (3,4). Although the exact mechanism of the occurrence of these discontinuation symptoms is still unclear, the symptoms are probably due to an abrupt decrease in available synaptic serotonin in the face of downregulated serotonin receptors (5). Findings that the re-introduction of an SSRI suppresses discontinuation symptoms within hours and that SSRIs with a shorter half-life cause discontinuation symptoms more frequently than those with an extended half-life, support this hypothesis (6-8). Tapering SSRI therapy, therefore, as opposed to abrupt discontinuation, has been recommended as part of routine practice by several guidelines and in the literature (1,9,10). However, there are, to our knowledge, no observational or experimental direct comparative studies to support the tapering recommendation. Besides the lack of evidence of a favourable effect of tapering, it is unclear how patients discontinue SSRI therapy in routine practice. The GPs may not be confidently aware of adverse events associated with SSRI discontinuation (11). In addition, patients may not always inform their physician about stopping SSRI medication (12) and discrepancies between instructions on the use of SSRIs and what patients remember being told have also been shown (13).

The aim of this study was therefore to examine the way in which patients discontinue SSRI therapy in clinical practice and to compare the effect of tapering with that of abrupt discontinuation on the occurrence of discontinuation symptoms.

Methods

Setting and design

Patients were included at 16 community pharmacies in the Netherlands between 1 December 2002 and 31 January 2003. The inclusion criteria for participation in the study were: male or female aged over 18 years, prescription duration of paroxetine, fluoxetine, fluvoxamine or citalopram of at least 2 months during the past half year and last dose of antidepressant between 2 weeks and 3 months prior to inclusion. Based on these inclusion criteria, potential patients were selected through the pharmacy information and administration systems. These patients were

contacted by phone to check for inclusion criteria and willingness to participate. Eligible patients received a pre-tested questionnaire and were asked to complete and return it within one week to the study coordinator. After one week patients were telephoned once, to check for any problems in completing the questionnaire. Ethics committee approval at this time was not required in the Netherlands for this type of study. Because there was no information available about the number of patients abruptly discontinuing therapy in daily life, it was not feasible to make a consideration of sample size. Therefore, the number of patients was based on and limited by the potentials of the participating pharmacies.

Outcome measures

Primary outcome measure was the number of discontinuation symptoms. The occurrence of discontinuation symptoms was assessed by means of a Dutch translation of the Discontinuation-Emergent Signs and Symptoms (DESS) checklist (14). This 43-item DESS-checklist was developed by Rosenbaum et al. based on an evaluation of signs and symptoms associated with discontinuation or interruption of SSRI treatment, as reported in the available literature. Patients were asked whether they had experienced one of the listed signs or symptoms during the first week after they had discontinued antidepressant therapy, but not during antidepressant use (i.e. newly occurring DESS events). In addition, patients were asked to indicate whether the specified sign or symptom was already present during the last two weeks of treatment (i.e. intra-individual change in the number of DESS events). Secondary outcome measure was the occurrence of a "discontinuation syndrome". Patients were classified as having experienced a "discontinuation syndrome" if the number of reported DESS events increased by four or more from during treatment to the week after discontinuation of treatment (14). Other questions were about reasons for discontinuation, impact on daily life, and patient counselling and education. Patients were asked to indicate the reason for discontinuation ("side effects", "no need for antidepressants", "feeling better", "ineffectiveness", "antidepressant used up", "forgotten and discontinued", "advice from others" or "other reasons"). Three questions were used to assess the impact on daily life. Patients were asked to rate on a 4-point scale whether discontinuation caused problems in their relationships with family or friends, with other people or in daily life and job activities ("no problems"; "minimal problems"; "moderate problems"; "severe problems"). Patients were also asked to rate their general functioning after discontinuing therapy on a 4-point scale ("excellent"; "good"; "reasonable"; "bad"). Finally, patients were asked to indicate whether they had received information about discontinuation symptoms at the start of therapy and whether they perceived this information as adequate or inadequate.

Determinants

The primary determinant of interest was the method of discontinuation SSRI therapy; abrupt discontinuation versus tapering. Patients were asked to indicate the way in which they discontinued their antidepressant: abruptly, using a self-made tapering schedule, using a GP-made schedule, using a psychiatrist-made schedule or using a schedule made by the pharmacist. Other determinants were gender, type of SSRI, age and knowledge of symptoms at start of therapy.

Data analysis

The Independent samples t test was used to compare the number of newly occurring DESS events and the intra-individual change in number of DESS events among groups of variables (abrupt discontinuation versus tapering; male versus female; paroxetine versus other SSRIs and knowledge of discontinuation symptoms at start of therapy versus lack of knowledge). The one-way analysis of variance (ANOVA) test was used to compare the number of DESS events between groups of age. The presence or absence of the discontinuation syndrome was treated as a binominal variable. Relative magnitudes of association between abrupt discontinuation versus tapering therapy and the presence of the discontinuation syndrome is expressed as a relative risk (RR) and 95% CI. The impact on daily life variables regarding problems in relationships and contact with other people were dichotomised as "problems" (moderate or severe) versus "no problems" (no or minimal). General functioning was dichotomised as "negative" (reasonable or bad) versus "positive" (excellent or good). All statistical analysis were performed using SPSS 10.0

Results

To check for inclusion criteria and willingness to participate in the study, a total of 105 patients were contacted. Of these, 20 could not be included: 6 were unreachable by phone, 12 were not willing or able to participate and 2 never actually started taking the antidepressant. Therefore, 85 patients fulfilled the inclusion criteria and were willing to participate – 74 (87%) of these patients completed and returned the questionnaire, of which 66 (78%) patients were eligible for analysis. Mean (±SD) age of the eligible patients was 46.3±14.0 years and 50 (76%) patients were female. Paroxetine was used by 46 (70%) patients, 7 (11%) used fluoxetine, 7 (11%) fluvoxamine and 6 (9%) citalopram. Median daily doses were 20 mg for paroxetine, 20 mg for fluoxetine, 100 mg for fluvoxamine and 20 mg for citalopram. Of all patients, 14 (21%) abruptly discontinued their antidepressant, 28 (42%) used a self-made tapering schedule, 20 (30%) a GP-made schedule and 4 (6%) a tapering

schedule made by a psychiatrist. The periods of tapering varied from two weeks to four months.

Table 1 lists the intraindividual change in number of DESS events after discontinuation and the number of newly occurring DESS events after discontinuation for different groups. Patients who abruptly discontinued therapy experienced significantly more DESS events than patients who tapered therapy. There is a trend for a significant adverse effect in patients who report a lack of knowledge of discontinuation symptoms at the start of therapy. No differences were shown for age, gender and prescribed SSRI. In 39 (59%) of all the patients, the "discontinuation syndrome" occurred. Abrupt discontinuation of antidepressant therapy has an adverse effect on the occurrence of the discontinuation syndrome (86% vs 52%; RR 1.6; 95% CI 1.2 to 2.3).

The most frequently reported discontinuation symptoms included nervousness or anxiety, irritability, bouts of crying or tearfulness, dizziness or light-headedness. Trouble sleeping, dizziness, confusion or trouble concentrating, headache, nausea and vomiting were the symptoms patients experienced as most serious.

Main reasons for discontinuing antidepressant therapy were feeling better (45%), side effects (24%), no need for antidepressant (15%) and ineffectiveness (8%). More than one reason for discontinuation was indicated by 36% of all patients. Of all patients, 38% has discontinued antidepressant therapy once before. Most patients discontinued therapy on their own initiative (83%) and/or on advice of their general practitioner (27%). Patients' social environments and pharmacists hardly played a role in this. Of all patients, 9% restarted their antidepressant and 27% considered restarting.

Of all patients, 38% were informed about the possible occurrence of discontinuation symptoms before starting their therapy: 27% received this information from the general practitioner, 5% were informed by the psychiatrist and 5% by the pharmacist. Knowledge of discontinuation symptoms influenced the way patients discontinued their antidepressant. Of the patients who were informed about discontinuation symptoms, 12% abruptly discontinued therapy, while in the group that was not informed 26% discontinued therapy abruptly. Of all patients, 49% perceived the information about discontinuation symptoms as inadequate.

An adverse effect on general functioning after discontinuation therapy was indicated by 83% of the patients abruptly discontinuing therapy and by 48% of the patients tapering therapy. Discontinuation influenced both daily and job activities: 45% of the patients abruptly discontinuing therapy and 26% of the patients tapering therapy experienced problems. Problems in relationships with family and friends were indicated by 29% of the patients abruptly discontinuing and by 24% of the patients who tapered their cessation. Finally, 33% of the patients who abruptly

Table 1 Symptoms following discontinuation of selective serotonin-reuptake inhibitor (SSRI) therapy

	Number of patients	Intra-individual change in number of DESS events [a]	p-value [c]	Number of newly occurring DESS events [b]	p-value [c]
		Mean (SEM)		Mean (SEM)	
Overall	66	6.5 (1.0)		7.2 (0.9)	
Way of discontinuation					
tapering	52	5.1 (0.9)	p=0.004	5.9 (0.9)	p=0.006
abrupt discontinuation	14	11.7 (2.7)		12.0 (2.6)	
Gender					
male	16	5.8 (2.3)	p=0.67	6.4 (2.1)	p=0.60
female	50	6.7 (1.1)		7.5 (1.0)	
Age (years)					
< 40	20	4.6 (1.7)	p=0.28	5.5 (1.6)	p=0.30
40-54	30	8.1 (1.7)		8.7 (1.6)	
≥55	16	5.9 (1.3)		6.6 (1.2)	
SSRI					
paroxetine	46	6.8 (1.2)	p=0.62	7.8 (1.1)	p=0.38
others	20	5.8 (1.8)		6.0 (1.8)	
Knowledge of symptoms at start therapy [d]					
yes	25	4.9 (1.2)	p=0.14	5.5 (1.0)	p=0.08
no	35	8.0 (1.6)		8.9 (1.5)	

a Intra-individual change in number of DESS events from treatment phase to discontinuation phase
b Number of newly occurring DESS events following SSRI discontinuation
c p-values assessed using one-way ANOVA for comparing the number of DESS events among groups of age and Indepent samples t test for comparing among groups for the other parameters
d Totals are less than 66 due to missing data

discontinued therapy and 16% of those tapering therapy experienced problems in contact with other people.

Discussion

Although guidelines recommend to taper SSRI therapy when discontinuing, this study shows that one in five patients abruptly discontinued their SSRI in clinical practice. Abrupt discontinuation of SSRI therapy caused a larger increase in discontinuation symptoms than tapering. This study also shows that abrupt discontinuation had an adverse effect on daily life activities and social functioning. An adverse effect of discontinuation has also been seen in other studies (4,7). Discontinuation symptoms may be misdiagnosed, leading to alternative pharmacological therapy or re-instatement of the antidepressant (4). In our study, several patients indeed restarted their therapy. Misdiagnoses may also lead to unnecessary diagnostics and accompanying costs (6,8,15). We suggest that knowledge of discontinuation symptoms and tapering strategies by both patients

and professionals can be an important factor in preventing the occurrence of discontinuation symptoms. In this study, patients who reported a lack of knowledge of discontinuation symptoms at the start of their antidepressant experienced a larger increase in symptoms after discontinuation. Only one-third of all patients were informed about the possible occurrence of these symptoms.

We have used three different outcome measures to assess the effect of discontinuation: intra-individual change in number of DESS events, number of newly occurring DESS events and the occurrence of the discontinuation syndrome. The number of patients having a discontinuation syndrome, an increase of DESS events by four or more after discontinuation, represents those patients who experienced a substantial negative effect of discontinuation. However, the discontinuation syndrome is a binominal measure and therefore less sensitive for changes, whereas the intra-individual change in number of DESS events and the number of newly occurring DESS events are continuous measures. The intra-individual change in number of DESS events reflects an overall effect of discontinuation, including positive effects of discontinuation, such as the disappearance of side effects. The number of newly occurring DESS events, however, reflects the effect of discontinuation itself. Therefore, the latter approach may be more appropriate with respect to the aim of our study, comparing the effect of tapering with abrupt discontinuation. Overall, the outcome measures we used appeared to be feasible and sensitive for changes in therapy. A doubling of symptoms between tapering and abrupt discontinuation has been shown, resulting in a convincing significant and clinical effect.

We would like to touch on also some limitations of our study. Patients were interviewed retrospectively, which may have introduced a recall bias. However, the negative effect of abrupt discontinuation is strikingly large, and it is not expected that patients who abruptly discontinued their SSRI would recall more symptoms than patients who taper of therapy. Selection of patients may have also introduced a bias. In view of the large number of patients willing to participate and completing and returning the questionnaire, and the characteristics of the patients, we think a selection bias is unlikely. There are no reasons to believe that the non-participating patients would differ from the participating patients in the number of discontinuation symptoms occurring. Finally, the numbers of patients using the various SSRIs were too small to show any difference among the different type of SSRIs.

One major strength of our study is that we used data from patients directly. Therefore, we were able to show how patients discontinue therapy in real life. To our knowledge, this is the first study that shows a remarkable number of patients discontinuing therapy abruptly, resulting in a rather adverse effect on patients' daily life. Although a prospective study would be of value in studying the effect

of discontinuation with respect to indication, type of SSRI and cumulative dose, the results of our study may not be undervalued. In conclusion, therefore, we urge to taper SSRI therapy in clinical practice to prevent unnecessary adverse effects of discontinuation. Patients' knowledge of discontinuation symptoms and how to discontinue SSRI therapy must therefore be improved.

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5 General Discussion

This thesis aims to understand why patients deviate from the prescribed and advised treatment with antidepressant drugs. During recent years many observational studies have revealed important quantitative information on antidepressant drug taking in daily practice. However, the considerations and decisions from a patient perspective that underlie patients' behaviour have been relatively absent in research (1-3). In this thesis, we explore patients' considerations and decisions within the framework of the course of antidepressant drug taking, consisting of three phases, namely initiation, execution and discontinuation of therapy (see Figure 1). Unravelling the complexity of the decision making process of patients based upon this course is of great value in understanding how patients' experiences, health beliefs and other patient factors affect the three phases of therapy. In this general discussion, we first discuss critical factors related to the initiation, execution and discontinuation phase of therapy. Second, we consider our findings in the context of improving care for patients who start a new course of antidepressant therapy. And finally, we would like to present our thoughts on the stimulation of research from a patient's perspective.

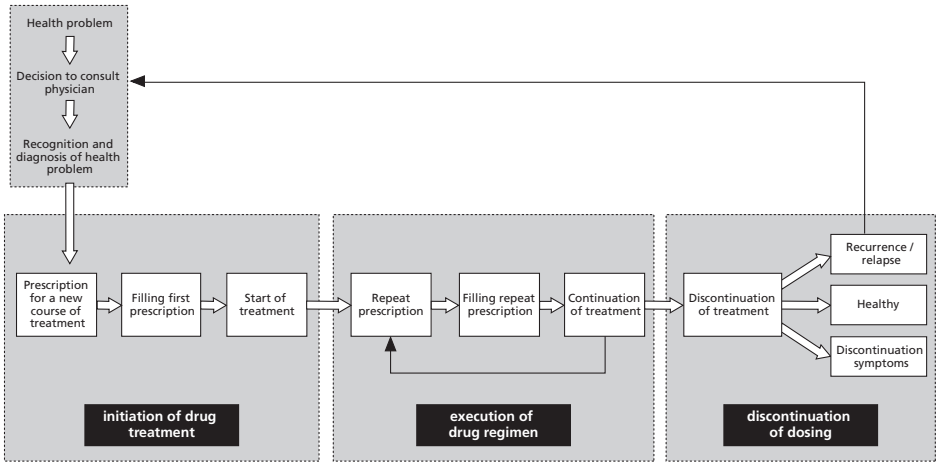

Figure 1 Course of antidepressant taking – initiation, execution and discontinuation

Critical factors related to the course of drug taking

Research within this thesis has revealed factors that are important in understanding patients' antidepressant drug taking behaviour. Table 1 gives an overview of patients' considerations that guide decisions about initiating and stopping antidepressant drug taking. Although most of the considerations play a role in each phase of the course of drug taking, certain types of considerations, as well as other patient factors concerned, are more prominent in a single phase. In this context, we found illness perception and severity, treatment needs and concerns, and patients' views on information to be crucial factors in the initiation of antidepressant

Table 1 **Considerations of patients that guide decisions on initiating and discontinuing antidepressant drug taking**

	Initiation of therapy	Discontinuation of therapy
Illness perceptions		
Cause of illness (biochemical vs. mental)	++	+
Identity and severity of symptoms	++	+
Personal consequences (stigma associated with mental illness, personal responsibility)	+	
Treatment needs		
Impaired social functioning; feeling guilty towards family and job	++	+
Perception of needing treatment and preferred treatment (own strength, psychotherapy, counselling or medication)	++	+
Receiving medication is relief; confirmation of having a serious problem	+	
Feeling better; feeling cured		++
Uncertainty about continued need for medication and contribution medication in recovery; testing efficacy medication by stopping		++
Feeling still unstable; uncertain consequences of stopping; worries of relapse		+
Treatment concerns		
Stigma associated with using medication; using medication is sign of weakness	++	+
Concerns about side effects:		
• due to previous experience, most often side effects occurring shortly after start (e.g. gastrointestinal side effects, palpitations)	+	
• social embarrassing side effects (e.g. weight increase, increased sweating, sexual dysfunction)	+	+
• psychiatric side effects (e.g. blunting of affect, not feeling like oneself, loss of creativity)	+	+
• long-term brain effects (brain damage, personality changes)	+	+
Fear of dependency (physical versus psychological)	+	+
Fear of discontinuation symptoms		+
Treatment experiences		
Troubling side effects:		
• short-term side effects	+	
• social embarrassing side effects		+
• psychiatric side effects		+
Delayed onset of action (feeling even worse due to side effects)		+
Lack of effect or insufficient effect		+

Rating of relevance of consideration in taking treatment decision:
+ = consideration is relevant in guiding the decision for most patients, or key for some patients
++ = consideration is key in guiding the decision for most patients

therapy. Fundamental in exploring the execution phase of antidepressant therapy are changes in patients' attitude towards antidepressant treatment in response to experiences while taking them. Furthermore, exploring the considerations that contribute to decisions to stop antidepressant drug taking, assessing whether patients taper treatment as opposed to abrupt discontinuation, and exploring the role of information in stopping treatment, are important to understand patients' behaviour during discontinuation of antidepressant therapy.

Initiation of antidepressant therapy

Previous research has shown that of all patients having an antidepressant dispensed at the pharmacy, up to one-third fill only a single prescription (4-7). In this thesis, we further separate the steps within the initiation phase of drug taking. So far, no studies have focused on patients who recognise they have a problem, decide to consult their physician and receive a prescription, but don't initiate treatment. We found that of all patients receiving a prescription for a new course of antidepressant treatment, four percent did not fill the prescription at the pharmacy and over twenty percent filled only a single prescription (Chapters 2.1 and 2.2). Furthermore, of all patients collecting a prescription at the pharmacy for a new treatment course, eight percent had not used a single tablet (Chapters 2.2 and 3.1). Apparently, many patients accept a prescription from their treating physician, but do not accept and initiate the treatment plan. Illness perception and severity, treatment needs and concerns, and drug information revealed to be important in initiation of therapy.

Illness perceptions and severity

Illness severity and perceptions of the illness by patient and physician are critical factors in the understanding of patients' behaviour towards the initiation of antidepressant drug taking.

Depression, anxiety, panic and obsessive-compulsive disorders (OCD) are the officially approved indications for the type of antidepressants studied in this thesis. However, our findings show that approximately half of the patients who did not initiate treatment were diagnosed by their physician as having a less specific indication for use of the antidepressant, including 'feeling depressed', 'sleeping problems', 'fatigue' or 'relational problems' (Chapter 2.1). In addition, the study in Chapter 3.1 in patients collecting a first-time prescription showed that one in five patients did not meet criteria for depression or anxiety, since the severity of the illness did not correspond to threshold scores for depression or anxiety. For these types of less specific indications, the effectiveness of antidepressants has not yet been established (8-11).

Little research has been done into antidepressant treatment decisions, and it is unclear whether patients initiate discussions with their physician about the need for treatment or for antidepressant medication in particular. We can only speculate on the reasoning of physicians to prescribe an antidepressant for the variety of psychological and social problems as seen in our studies. Studies performed in this area and within this thesis mainly focus on treatment with antidepressants in general practice. General practitioners (GPs) believe they do not easily decide to prescribe antidepressants. Their decisions about whether an antidepressant would be an appropriate form of treatment are shaped by a set of rules based on clinical and social criteria (12,13). However, a study by Kendrick et al. showed that although GPs base their prescribing decisions on the perceived severity of depression, they do not accurately identify which patients are likely to benefit from treatment. GPs' ratings of severity did not agree well with a validated screening instrument for depression (14). Physicians generally see depressive symptoms against a background of a patient's family history, physical illness, life events, and degree of disability (15,16). GPs seem to use non-specific clinical clues such as distress and impairment, as well as their knowledge of the patient in diagnosing depression (17). Mild depressive symptoms and psychological or emotional problems can be associated with significant functional impairment, which physicians may feel inclined to address (15,17). Treatment with an antidepressant sometimes seems to be given 'palliatively' in an attempt to ameliorate troubling symptoms, and may be seen as subsidiary to supportive care (16). An interview study by Maxwell indicated that GPs consider diagnosing and managing depression to be problematic, whereas they perceive diagnostic tools to be of little use (18). In their view, the only way to help patients is to medicalise the problem and prescribe medication. In this context it is important to note that GPs point out several barriers for improved care, such as pressure of time and lack of other forms of help (12,13,19). In a study by Pollock & Grime, GPs expressed the view that having more time with their patients, either in active counselling or a more passive listening role, could reduce the need for antidepressants (20). Other studies addressed patients' influence by initiating discussions on antidepressants as possible treatment. Tentler et al. showed patients' requests for medication prompting the physician to err on the side of overtreating versus careful review of the clinical indications (21). In another study, they showed patients' requests to increase prescribing for adjustment disorder with depressed mood, for which antidepressant use is debatable (22).

A further important finding relates to the perceptions of illness and symptoms by patients themselves. Determining how patients understand and define depression is likely to be critical in understanding how they manage the illness and cope with treatment (23). Results from a recent meta-analysis suggest that disease severity,

and patients' awareness and understanding of it, are major factors that need to be addressed effectively in order to foster the way patients follow treatment advice (24). Patients form their own personal models of illness that help them make sense of the situation and guide their own coping responses, e.g. accepting or not accepting the diagnosis, initiating or not initiating treatment (25). Patients who feel that diagnosis, explanations and information received fit with their perspective of the problem are more inclined to concord with medication (26). A patient's model of illness comprises his beliefs about the identity of the illness, cause of the illness, likely duration of the symptoms, personal consequences and perceived controllability (27). Illness identity refers to the label the person uses to describe the illness and symptoms. The cause dimension represents the beliefs about what caused the illness or symptoms, and likely duration refers to the patient's beliefs about how long it will last. The consequence of the illness refers to beliefs about the impact of the illness on quality of life or how it affects patient's functioning, and controllability represents beliefs about how the problem can be controlled, personally or by treatment. Research within this thesis revealed identity, cause, consequences and controllability of the illness to be key dimensions. Consequences and controllability will be discussed below in relation to treatment needs and concerns.

We found that patients and their physicians differ in perception of symptoms, as reflected in the reasons for use reported by both. Unlike their physician, patients more often reported less specific symptoms as reason for use, such as stress, fatigue or restlessness (Chapter 2.2). In addition, patients considered their problem to be less serious compared to their GPs. This discrepancy in perception of symptoms was particularly prominent in the group of patients who declined treatment shortly after receiving the first prescription. Furthermore, patients who discontinued treatment within six months after start showed a greater discrepancy between illness severity according to standardised depression and anxiety scales and patients' perception of symptoms than patients who continued drug taking (Chapter 3.1). One possible explanation could be the lack of awareness and understanding of the nature and severity of the illness among some patients (28,29). Since physicians do not always discuss the diagnosis of depression with the patient, patients may underestimate the severity of the illness. Van Vorhees et al. found that non-acceptance of diagnosis was associated with low symptom severity (30). Badger & Nolan showed that the severity and length of the depressive illness affects people's initial concordance with medication (26). Another plausible explanation refers to the perceived negative consequences of accepting the diagnosis of an emotional disorder. The denial of the disorder is considered to be a major obstacle to treatment (31,32). Patients regularly have difficulty accepting the diagnosis of depression and tend to label

their symptoms with a less loaded term, such as hormonal disbalance or burn-out (Chapter 3.2). Generally, emotional disorders are strongly associated with negative views (18,33-37). Depression is not seen as a real illness because it lacks physical attributes. Patients are ashamed to admit to psychological symptoms, and accepting the diagnosis usually affects their self-esteem. During interviews with patients as described in Chapter 3.2, they often expressed a fear of being labelled as a person with a stigmatising emotional or psychiatric disorder. A study by Weich et al. identified two divergent views about depression (35). The first reflected a view of depression as a permanent, disabling and stigmatising mental breakdown from which there was little prospect of recovery, while the second concerned a more sympathetic view of depression as a medical condition that could affect anyone and from which recovery was possible with support and help.

Patients' view on the cause of the illness is a further key mediating how patients cope with their problems. Patients most commonly endorse multiple causes of depression, including hereditary of a depressive tendency, depression as character trait, and depression as a natural reaction to adverse circumstances such as bereavement or work/relationship difficulties (23,38). In their discussions with patients, physicians often address the biochemical model of depression as an illness mediated by decreased concentrations of neurotransmitters, and antidepressants increasing the neurotransmitter concentrations back to normal (34,39). Patients sometimes find this model helpful in making depression a physical rather than a mental disease, as this helps to remove concerns about personal responsibility or stigma, and makes the illness more acceptable. Van Vorhees et al. showed those agreeing with a biological cause of depression are most likely to express intent to accept a physician's diagnosis of depression (30). We also showed that the serotonin imbalance theory is helpful in accepting the diagnosis and the treatment for part of the patients. Others, however, were not entirely convinced by the biochemical explanation and were seeking to identify the cause of their illness within their personality or difficulties in their personal life (Chapter 3.2). Although this biochemical explanation helps to remove concerns about personal weakness, we believe it should be used cautiously. Patients use and interpret the model in different ways, and it may reinforce patient's dependency on medicines rather than seeing antidepressants as part of the solution (39).

In conclusion, it is important for physicians to explore people's attitude towards the illness prior to consider treatment. As argued by Dowell & Hudson, if patients do not accept their illness they are unlikely to accept its treatment (40).

Treatment needs and concerns

Patients' perception of needing drug treatment and their concerns about antidepressant medication vary largely between patients and influence the decision on initiating drug taking.

Patients seek many different ways to cope with their health problems, and have particular views on treatment options. The vast majority of patients in general practice prefer treatment approaches for emotional problems that go beyond antidepressant medication (19,41). Antidepressants are rarely mentioned as a preferred treatment, depressed patients strongly prefer psychotherapy and counselling. In most cases, the patients' preferences for treatment of emotional problems were not in accordance with what physicians consider being effective treatment (19). The most important demand patients express is more time with the physician, since they believe more information and advice would help them (19,31,42). Most patients just expect the GP to listen to their problems and hope for an understanding attitude (13). Our data seem to confirm that patients do not necessarily expect to receive a prescription when consulting the physician. Not wanting to use medication for treating their symptoms was reported in the studies described in Chapters 2.2 and 3.1 as major reason for not starting use. The interview study in Chapter 3.2 revealed that patients' participation in the prescription decision varies largely between patients. Most patients described their situation before consulting the physician as one of distress and hopelessness. In some cases, patients felt that they had no other option than accepting the prescription when their physician offered to prescribe one. They often did so with relief. In a study by Maxwell, women accounted for their acceptance of antidepressant medication as a sense of duty towards other family members (18). Many patients had initial reluctance and needed to be convinced of the necessity of treatment (Chapter 3.2). GPs play an important role in resolving patient dilemmas about starting antidepressants, by providing reassurance and addressing concerns (18,43). Grime & Pollock also showed patients to be either relieved to be taken seriously and to be provided with a way out, or to resist or even reject treatment (39).

People have ideas and beliefs about medicines that influence their decisions on medicine taking. At the start of antidepressant treatment, patients report a variety of views. Beliefs about medication were not all negative. The study in Chapter 3.2 showed that some patients hardly have any concerns and simply feel that emotional problems must be treated just like physical problems. In their view, using antidepressants to increase serotonin levels is as normal as using medication to lower cholesterol levels. However, there is a widespread belief in our society

that medicines create dependence and that being on chemicals is not a good thing (33,44). In our and other studies, many patients showed to be reluctant to consider taking antidepressant medication (37,39,42). Patients are generally keen to portray themselves as the type of people that do not resort to medication use, or would rather not have to resort to medication use if they could help it (18). Needing a drug to function normally feels like a sign of weakness, and patients often feel guilty and ashamed. A study by Knudsen et al. showed women to perceive receiving antidepressant medication for their illness as a double stigma. Next to the risk of stigmatisation because of the illness as such, they also fear stigmatisation due to the reputation of the medicine as 'happiness' pill (34). Perceived stigma about both illness and treatment assessed before starting has shown to predict subsequent antidepressant medication adherence (45).

Many patients express concerns about side effects, sometimes due to previous experiences with troublesome side effects. Patients also have concerns about long-term effects on the brain, particularly fearing changes in personality traits. Patients worry that antidepressants blunt them too much with deleterious effects on function and cognition, particularly grieving (37). Fear of side effect was reported as the main reason for not initiating antidepressant use (Chapters 2.2 and 3.1). Moreover, patients worry about addiction, believing antidepressants to be similar to benzodiazepines. Some are aware of the need for tapering the antidepressant and the associated withdrawal symptoms, and believe this is a sign of addiction (Chapters 2.3 and 3.2). Next to the fear of physical dependency, patients' concerns often focus on psychological dependency; the fear to rely on a drug rather than on themselves. This fear is an issue of which healthcare professionals are often unaware (39). Healthcare professionals do seem to address the issue of physical dependency in their discussions with patients, but hardly pay attention to patients' fear of psychological dependency (Chapters 2.3 and 3.2).

Finally, the decision to start and continue drug taking is influenced by the way in which patients evaluate their personal need for medication relative to their concerns about potential negative effects of taking it (1,46). In making the decision, patients evaluate whether the physicians' advice to start drug taking makes sense in the light of their own understanding and beliefs about the illness and treatment. Patients who had dispensed a prescription for a new antidepressant treatment at the pharmacy but did not initiate drug taking, had at start a rather negative attitude towards medication and were not very much bothered by the view of their GP on taking the medicine (Chapter 3.1). Patients hold sets of beliefs and theories about their illness and treatment, and these are moderated by information from others, such as the physician, pharmacy, family members and the media (2).

Views on information

Based on their preferences for involvement, patients need balanced information addressing concerns and uncertainties being able to consider the consequences of taking or not taking antidepressant medication.

People have a broad range of information preferences that vary at different times and for different reasons (47). Also, patients and healthcare professionals differ in their priorities for information about drug treatment (48). Physicians discuss potential benefits of treatment more than potential harm, precautions, or risks, even though patients see these topics as essential (48,49). A considerable number of patients reported that side effects were not discussed by their GP before prescribing antidepressant treatment (50). The failure to explore patients' beliefs about medicines and to inform them of the pros and cons of treatment has been found to lead to misunderstandings and unaddressed concerns (51,52). Garfield et al. showed that a large amount of information is required to support patients initiating treatment with antidepressant medication (53). Chapter 2.3 also showed that the current information patients receive does not meet their needs. Patients make the decision to start antidepressant use, although they feel they lack adequate knowledge. Many of them require more information to feel confident that starting antidepressant use is inevitable. Unmet information needs include concrete and practical information on adverse effects and the delayed onset of action that is expected, addressing concerns about physical and psychological dependency and the potential harm of long-term treatment. Discussing the potential impact of antidepressant treatment on patients' lives would make them feel more prepared and supported during use.

Although verbal information is the information of choice, many patients consider written information about medicines as vital especially at the stage of initiating treatment (54). The advantage of an information leaflet is that the patient is able to return to the information afterwards, when they have questions or feel unsure about certain effects experienced with medication. However, even more than verbal information, written patient information has been criticised for being too medico-centred. The content often centres on topics of importance to professionals, but may not reflect patients' actual information needs (55-57). Patient information leaflets present information about medicines often with great certainty, simplicity and optimism (54,56,57). Leaflets usually do not consider patients' concerns and uncertainties, thereby not supporting patients' involvement in treatment decisions (56). Grime & Pollock showed the gap between a medico-centred antidepressant information leaflet and patient experiences with antidepressants (38). They argue that the main goal of the information leaflet is reassurance about the effectiveness

and safety of antidepressants and to promote adherence to treatment. The biochemical theory of depression being caused by a serotonin imbalance is used to emphasise the need for drug treatment. Other current information leaflets do also often address the biochemical model of depression to explain the need for medication. However, leaflets generally do not address the concerns, misgivings and uncertainties that many patients have. They rather downplay the problems patients experience with treatment, such as the burden of side effects, lack of therapeutic benefit, and coming of medication. In addition, Chapter 2.3 showed patients to criticise the written information as being difficult to interpret, raising new questions, or being too general and not sufficient specific for their own situation.
Next to the verbal information from the physician and the information leaflet, patients reported receiving antidepressant information from other sources, such as friends or family members, the Internet or the lay media (58). Studies in other diseases showed that information about peoples' experiences is important to patients and is often used in addition to professional information (59,60). Users of antidepressant medication also seem to appreciate the direct accounts of peoples' experience of depression and its treatment. Information leaflets which draw on patients' experiences would recognise the reality of patients' use of antidepressants. Grime & Pollock therefore recommend improving leaflets accommodating experiential patient knowledge (38). This would enable patients to engage in more concordant consultations with health professionals, initially and during subsequent contact with healthcare professionals.

In general, patients do not consider the pharmacy to be an important source of antidepressant drug information (Chapters 2.3 and 2.4). Patients feel that their physician is the most appropriate person to inform them about antidepressant drug taking. As shown by other studies as well, patients are unfamiliar with the pharmacist's task as information provider and caregiver (61,62). Patients report several barriers to a wider role of the pharmacy as source of drug information. They experience lack of time and privacy as barriers to an improved communication in the pharmacy. Also, the patients in our study consider the pharmacy information as impersonal and far too protocolised (Chapter 2.3). Although community pharmacists express a positive attitude towards a wider role in the care of depressive patients, their reported activities show that pharmacists are doing little as intermediaries between patients and physicians (63). Pharmacists themselves reported a reluctance to engage in discussions with antidepressant users, because of concerns that this might not be welcomed by the patient (64). There is evidence that community pharmacists offer advice to patients presenting with a first-time prescription for an antidepressant (63,65). After the use has started, pharmacists appear to have less involvement (63-65). This is a shortcoming, as providing all information at the initial contact is not

appropriate. Patients report to have difficulty recalling the information received at start of treatment and timing is therefore important (53). Telephone calls from pharmacists soon after starting treatment can reduce patients' non-adherence, their medicine-related problems, improve their knowledge and stimulate feedback to pharmacists (66,67). Such feedback may help pharmacists identify and address patients' misconceptions, concerns and progress with antidepressant therapy. Routine counselling when the antidepressant medication is dispensed for the second time, as currently being implemented by many Dutch pharmacies, is thus important.

Studies about communication with patients are often based on the assumption that more information leads to better adherence to treatment instructions. Some studies showed an effect of specific educational messages and good patient-physician communication on adherence to antidepressant treatment (68-70). Overall, however, giving information does not necessarily change patients' antidepressant drug taking behaviour (54,71-77). Bollini et al. stated in their review that the base for evidence of the recommendation for patient education to improve adherence is rather tenuous (78). Whether the lack of a positive effect on adherence is disappointing depends on the role we attribute to patient information. Information on medicine use is increasingly viewed as a requisite for informed decision making about treatment (54,57). Patients increasingly want to understand their condition better and be more involved in decisions about treatment (79). However, patients cannot express informed preferences unless they are given sufficient and appropriate information. Physicians therefore need to identify and understand patients' views and explain the relevance of treatment, while patients gain an understanding of the consequences of taking or not taking the medication (56,80). In this respect, we need to be aware and respectful of better-informed patients deciding that they do not want any drug treatment at all (80). Finding out how much the patient wants to be involved in decisions about treatment is important. Some patients wish to make their own decisions based on appropriate and balanced information, while others prefer to delegate the decisions to professionals without requiring further information (81).

Execution of antidepressant therapy

Experiences with treatment, side effects and effectiveness in particular, need to be evaluated and discussed during treatment. Patients' attitudes towards antidepressants are not fixed and change over time in response to the experiences of taking them.

It is obvious that the burden of side effects reported by patients is substantial. Antidepressant side effects may occur immediately after start, while it usually

takes some weeks before patients experience improvement of symptoms (82). Goethe et al. showed that onset of side effects occurred within the first two weeks of treatment for more than two-third of patients reporting side effects (83). Gastrointestinal disturbances such as nausea and diarrhoea, dry mouth, drowsiness, anxiety and tremors were reported to occur within the first two weeks. Side effects appear to be difficult to tolerate as they often make patients feel even worse with treatment. Patients reported side effects that occurred shortly after start as the major reason to decline treatment (Chapters 2.2 and 3.1). Although incidence of side effects is highest at the onset of treatment and most are believed to be transient, many patients appear to be bothered by the same side effects after the first weeks of treatment (84,85). During the first three months of treatment, over 4 out of 5 patients taking antidepressants described at least one side effect and over half experienced at least one side effect that was considered bothersome (83,85). The most commonly reported side effects differ between studies, but drowsiness, dry mouth, sexual problems, headache, dizziness, nausea, anxiety and sweating are generally the most frequently occurring (50,83,86,87). Yet, the most frequent side effects are not necessarily the most bothersome. Rash, sexual dysfunction, weight gain, insomnia, anxiety and blurred vision appear to be the most troubling persistent side effects for patients ((83,86) and Chapter 3.3).

There is a gap between the physicians' and the patients' perception of side effects. First, the burden of side effects is greatly underestimated by physicians (88). Although physicians are knowledgeable on side effects related to SSRI use, they underestimate their frequency and impact (85). We found that patients and healthcare professionals differ in the nature of side effects reported to a reporting system (Chapter 3.3). Apparently, patients and professionals differ in which type of side effects they consider to be bothersome and/or relevant to report. Patients more frequently report those events that may be less tangible and visible to professionals, such as sleeping problems and apathy. Healthcare professionals may also consider these types of side effects reported by patients with an emotional disorder as a symptom of the disease rather than as one related to the medication. Bolling & Kohlenberg found unwanted psychiatric side effects to be just as important as physical side effects when patients report reasons for stopping SSRI treatment (89). Patients were not primarily concerned with known physical side effects, but seemed instead to be concerned with more subtle psychiatric side effects, such as narrowed range of affect, not feeling like oneself and loss of creativity. Conrad showed that patients are more likely to alter their medication practice when side effects hinder their ability to participate in routine social affairs (44).

Communication between patients and physicians during treatment about side effects seems to be poor. In clinical practice, benefits of the medicine, not side effects are often the focus. Physicians and other healthcare professionals seem to

require smaller benefits before starting drug treatment than patients (90) During treatment patients sometimes feel that physicians merely concentrate on the effectiveness of the treatment, while ignoring their complaints about troubling side effects (Chapter 3.2). Haslam et al. stated that patients feel poorly informed about side effects because they were unprepared for the fact that the medication made them feel worse initially (91). In other studies only half of the patients reported to have discussed side effects with their physicians during the first three months of treatment (68,85). Furthermore, Bull et al. showed that discussing the adverse effects occurring during treatment is associated with less premature discontinuation of the antidepressant (68). Moreover, patients whose side effects are as described by their physician, feel their confidence in the physician and the medication increase, as this confirms that their physician is knowledgeable about the medication (26). It is, however, understandable that neither physicians nor patients spontaneously discuss all embarrassing or socially unacceptable side effects. For example, sexual dysfunction is often troubling for patients but at the same time is less likely to be discussed openly. In a study where both patients and physicians were asked if sexual dysfunction as a side effect was discussed during consultation, the results demonstrated a clear disparity (92). Two-third of physicians said they had mentioned sexual dysfunction as a side effect, whereas only 16% of patients said that their physician had mentioned it.

Perceptions of treatment do not develop in isolation (93). Patients' attitudes towards antidepressants often change in the light of further knowledge and experience with antidepressants. Patients who feel reluctant initially may become more positive about antidepressants as an effective and acceptable treatment in the short term. Other patients, even if they were positive in the beginning, were put off by troubling side effects or lack of any noticeable effect (39). Moreover, patients' beliefs can influence the appraisal of the effects of treatment. For example, patients who have strong concerns about potential side effects prior to treatment appear to be more likely to experience adverse effects of treatment (93). Also, when patients begin to feel better, there is a great disparity in how patients appraise their improved situation (Chapter 3.2). Patients may feel better, but still feel unstable. For these patients, feeling good is often a justification for continuing antidepressant drug taking. Other patients, however, particularly feel uncertain about whether, or how much, antidepressants have contributed to their recovery. Changes in their personal circumstances, starting physical activities or simply the natural process of recovery may be plausible explanations as well. These patients feel reluctant to take antidepressants when not being confident that they really need treatment. In Chapter 3.1, we found that health beliefs and perceived illness severity at start influence patients' decisions about treatment, being either not initiating, discontinuing, switching or continuing

antidepressant medication. Moreover, beliefs changed by patients' experiences with treatment over time. Patients who did not initiate or early discontinued drug taking developed more negative beliefs about treatment. Patients who continued antidepressant treatment developed more positive beliefs about treatment, while their concerns decreased. Remarkably, the initial discrepancies between users and non-users which were present at start, became more pronounced over time.

Discontinuation of antidepressant therapy

The decision to discontinue antidepressant drug taking is a complex and multifactorial process; patients often take this decision under less than favourable circumstances, while lacking adequate information and counselling.

Numerous studies have shown that the majority of patients do not continue to take their medication for the length of time as recommended by guidelines. The discontinuation rates appear to be greatest during the first month of treatment and continue at a slower but steady rate thereafter. Approximately one-third of patients discontinue treatment within one month of starting (4,6,7,69,94); between one-third and half of patients discontinue within three months (7,69,72,94-96); and half to almost three-quarters stop taking antidepressants in the first six months (5,97-100). The discontinuation rates we found in the study described in Chapter 3.1 were somewhat lower, which may be due to the selection of patients. In general, patients willing to participate in research may have a more positive attitude towards antidepressant and therefore more likely to continue treatment. Nevertheless, we also showed that almost half of patients discontinue use within six months, of whom most within the first two weeks.

Reasons why patients stop antidepressant medication are many and they vary with time (84,101). The main reasons to stop treatment in the first weeks may differ from those dominating later on during treatment. A study by Maddox et al. showed that main reasons to stop treatment in the early phase were side effects and lack of efficacy, while main reasons for stopping later on were feeling better, fear of dependence or not believing in drug treatment for depression (96). This study, however, followed patients only over 12 weeks of treatment. In a study by Demyttenaere et al. which followed patients over 26 weeks, the most frequently cited reasons for stopping treatment were feeling better (55%, mean time to discontinuation 11 weeks), and side effects (23%, mean time to discontinuation 6 weeks) (97). We were able to further differentiate the time-course of the reasons for discontinuation in Chapter 3.1. Almost half of the patients stopping treatment did so within the first two weeks, mainly due to the occurrence of side effects. From six weeks on most patients stopped treatment because they felt better and believed

that they do not need treatment anymore. Switching to other antidepressant medication was due to either perceived lack of effect, side effects or both.
It is important to note that merely describing the reasons for discontinuing treatment often oversimplifies patient's decision making on discontinuation. Patients are asked for their main reason for stopping, but reasons often interfere which each other and the way how patients interpret treatment effects and attribute the reason for discontinuation is influenced by patients' beliefs about the illness and medication. For example, the discussion on the relationship between side effects and non-adherence is more complex than often suggested (101). Side effects are common reasons for patients to discontinue drug taking, but experiencing medication side effects is not necessarily a predictor of changes in drug taking (26,101). Goethe et al. demonstrated that factors other than the presence or absence of side effects per se play a significant role in discontinuation of treatment (83). When patients report side effects as reason to stop treatment, they often give, at the same time, evidence of a more complex decision making process, in which lack of effect, aversion towards medicine use and fear of dependency play a role as well (Chapters 3.1 and 3.2). If a patient is more satisfied with what the medication is doing, she/he may be more able to tolerate side effects if they occur. Patients may interpret the experience of side effects of treatment as a sign that the drug is working or accept the side effect as an unavoidable aspect of drug taking. Patients' beliefs about the illness and treatment also seem to have a relevant influence in relation to perceived benefits of treatment. Patients who labelled their symptoms with a less specific term, such as feeling down, fatigue or sleeping problems, were less likely to continue treatment for the six months duration recommended for treatment (Chapter 3.1). When symptoms remit, some patients belief they are cured and do not need treatment anymore (Chapter 3.2). Patients feel uncertain about whether taking antidepressant medication has led to an improvement in health, or they are unsure whether continued use is necessary (43). Studies showed patients discontinuing treatment as an experiment to test the efficacy of the medicine and to discover the extent to which the tablets were still needed (31,39). Other patients fear that they become dependent on the medicine, or believe they come immune, when they take the medicine too long or too often (102). If patients feel dependent on and controlled by medication, it is not surprising that they seek to avoid their drugs.

Following termination or interruption of treatment with antidepressant medication discontinuation, discontinuation symptoms may occur (103-106). These symptoms typically appear within three days of stopping medication or reducing the dose. Discontinuation symptoms have been reported with all classes of antidepressants, and they may be associated with significant somatic and psychological distress (107,108). Different symptom clusters, or discontinuation syndromes, have

been described for SSRIs, TCAs, monamine oxidase inhibitors and the atypical antidepressants mirtazapine and venlafaxine (103,106). The SSRI discontinuation syndrome includes a state of disequilibrium (dizziness, vertigo, ataxia), gastrointestinal (nausea, vomiting) and flu-like symptoms (fatigue, lethargy, myalgia and chills), as well as sensory (paraesthesia, sensation of electric shock), and sleep disturbances (insomnia and vivid dreams) (107). While the SSRI discontinuation syndrome is usually transient and mild, symptoms at times can become serious (107,109). In most cases the symptoms resolve spontaneously in one week, but occasionally they can last for several weeks (100,106).

The discontinuation syndrome has gained attention over the last decade. However, few systematic and controlled clinical studies are available and most findings come either from case reports, discontinuation phases of clinical efficacy studies, or short-lasting interruption studies (103). These studies showed the discontinuation syndrome to be more common in patients discontinuing paroxetine and venlafaxine, antidepressants with relatively short half-lives, than in those stopping fluoxetine (105,108,110-112). Tapering the dose, as opposed to abrupt discontinuation, has been recommended as part of routine practice, but there have been no clinical studies to support this or to guide the duration of tapering (8,113). Schatzberg et al. suggested to collect data from patients in naturalistic settings since this may help answering some of the questions that might be difficult to address in the context of clinical trials (114). Analysing calls from a telephone medicines information service line showed that patients calling about antidepressants called about discontinuation three times as often, and reported a problem with discontinuation five times more often, compared to patients who called about non-psychiatric medicines (Chapter 4.1). In order to provide appropriate advice it is relevant to know how patients discontinue treatment in practice. As yet, it is unclear whether patients are aware of the need to taper, whether they indeed do taper treatment, and whether discontinuation of treatment causes a significant burden. We asked patients in clinical practice who recently discontinued their SSRI therapy about their experiences with discontinuation (Chapter 4.2). One in five patients had abruptly discontinued their therapy. Abrupt discontinuation caused a larger increase in discontinuation symptoms than tapering, and had an adverse effect on daily life activities and social functioning.

Remarkably, patients often discontinue treatment on their own initiative without informing the prescribing physician. Only one-third of patients stopped treatment using a tapering schedule made by their prescriber (Chapter 4.2). Demyttenaere et al. confirmed the limited role of the physician. In their study, only 9% stopped treatment following advice from their physician (97). Initially, two-third do not feel

the need to inform their physician of their decision to stop (68, 96). At six months a quarter of patients still stated that their physician did not know that they had discontinued their medication (97). Of those filling only a single antidepressant prescription at the pharmacy, as many as half did not inform their physician (Chapter 2.2). Furthermore, of all individuals who reported discontinuation of therapy as a result of side effects, one-third did not inform their physician (Chapter 3.3). Demyttenaere et al. suggest that whether or not patients inform their physicians depends on the patients' reasons for discontinuation and patients' perception of their relationship with their physician (97). The more a reason could hurt physicians' self-esteem, the lower the percentage of patients informing the physician. It seems more difficult to inform the physician about the drug being ineffective or the desire to solve the problems without drugs, than to inform the physician about feeling better. Also, the more empathetic the physicians' attitude was perceived to be, the higher the chance that patients informed their physicians. In their study of patient views on discontinuing long-term use, Leydon et al. noted a need for regular review. Patients need GPs to initiate discussions about the possibilities of stopping throughout the course of treatment (43). Knowledge of discontinuation symptoms and tapering strategies also seems to be an essential factor. Being aware of this influences the way patients discontinue their antidepressant, however, only one-third of all patients was informed about the possible occurrence of discontinuation symptoms (Chapter 4.2).

Unfortunately, current patient education materials do not advice patients on how to taper antidepressant treatment, that is the length of time over which it should occur and the minimum dose that one should taper to. We believe this is an important shortcoming. Much of the focus in patient information leaflets is upon reassuring patients about the effectiveness of treatment and to support adherence (38,54). In clinical practice, however, patients do not always follow treatment advice and frequently discontinue antidepressants on their own initiative without telling the prescribing physician. This may lead to unwanted situations in case patients abruptly stop treatment and discontinuation symptoms occur. Discontinuation symptoms include changes in mood, affect, appetite, and sleep, and patients may misinterpret the symptoms as a relapse or recurrence of their illness and unnecessary restart the use of the antidepressant (103). Warner et al. recommend health professionals to be alert to times when patients need guidance on discontinuing an antidepressant or when they are likely to discontinue an antidepressant on their own (106). In addition, Schatzberg et al. recommend physicians to educate patients on the management of the discontinuation syndrome prior to treatment or early in the course, and to remind patients frequently about these issues during treatment (114).

Furthermore, we believe written information materials should address the pros and cons of discontinuing antidepressant drug taking and provide practical advice on how to discontinue treatment.

Implications for practice

Healthcare professionals should inform patients of the pros and cons of taking or not taking antidepressant medication, involve them in the treatment decision, reflect progress with treatment over time, and elicit considerations as to whether continue or discontinue drug taking.

In addition to previous studies, this thesis shows that many of those who receive prescriptions for a new antidepressant course never initiate drug taking, discontinue treatment early without discussion with their physician, or abruptly discontinue drug taking rather than tapering. The important question here is whether the deviation from treatment guidelines and professional advice is a problem, and if so, how we should deal with it in practice. There is no easy answer.

We have shown that patients do not initiate treatment because they believe they are not depressed or have concerns about the drug. Patients discontinue treatment due to troublesome side effects or because they believe they are cured and feel they need no treatment anymore. Because patients are not aware of the need for tapering, they also regularly discontinue treatment abruptly. Hence, most patients make these decisions under less than favourable circumstances, lacking adequate knowledge and counselling by physician or pharmacist. This may result in unnecessary suffering from the illness, incomplete remission of symptoms or relapse, occurrence of discontinuation symptoms, ignored troublesome side effects, or eventually, losing trust in one's physician or in drug treatment. Moreover, as argued by DiMatteo, a medical visit that results in non-adherence is, at least partly, wasted (115).

The role of antidepressants in treatment is still under debate. Underrecognition, underdiagnosis, undertreatment, overprescribing and medicalisation of unhappiness have all been discussed in the context of treatment of depressive and anxiety disorders (14,16,17,29,116-124). Social pressure is believed to prompt people seeking a drug from their physician, while commercial pressure encourages to medicalise unhappiness (125). Pharmaceutical companies have been criticised for sponsoring the definition of diseases and promoting them to both prescribers and consumers (126). 'Social phobia' could be seen as the process of medicalising shyness, from a personal difficulty to a medical problem, for which drug treatment is seen as imperative (127). Another example is the presentation of the biological basis of depression. Since the nineties, serotonin deficiency theories have been

widely promoted to physicians and patients, suggesting that antidepressants are needed to increase the levels back to normal. Furthermore, in the professional and lay media, depression is regularly defined by promoting checklist diagnosis and counting symptoms (128).
A recent meta-analysis has shown that antidepressants are as effective as placebo in patients suffering from mild to moderate depression, which gave rise to further debate about the value of antidepressants in the majority of patients receiving them (11). In the treatment of major depression, however, it is obvious and accepted that antidepressants have an important role (8,10,129). This complex picture of the role of antidepressants in treatment is also seen in our studies. Part of patients were not depressed or anxious and prescribing antidepressant medication is therefore of questionable value (130,131). Others rather preferred other treatment options that go beyond medication. On the other hand, there is no doubt that some patients would have benefit from continuing to take antidepressant treatment longer than they currently have. It is beyond dispute that current antidepressant treatment practice is far less from optimal, yet we should prevent to consider non-adherence as the primary problem. Up to now, the majority of research and the subsequent recommendations are based on the assumption that the patient is expected to comply with the instructions (102,132). Non-adherence is seen as the result of patients' incompetence, and in particular their apparent inability to recall and understand the instructions they are given (57). This approach did not bring us any further as adherence to drug treatment did not really change over the years (115). For patients, adherence is not an issue; they make decisions based upon their beliefs and information at their disposal. In this thesis, we have shown that patients often make an intentional decision to decline treatment, but they regularly do so without the appropriate tools and adequate counselling. This is what we should address.

It is increasingly recognised that the key to improving medicine use is involving patients in decisions about treatment. Concordance and shared decision making are the terms frequently used to describe the shift in how we think about prescribing medicines. In fact, the model described for reaching concordance in consultations is the same as the one that has been described for shared decision making (133). The healthcare professional and the patient share their knowledge and experiences with each other so that an understanding can be reached and a decision about the management of the illness can be made. Effective communication is an essential element of both concordance and shared decision making. Communication is vital in order to elicit patients' beliefs and preferences about their illness and the medication that they are prescribed. The term concordance has its origin in the UK and is generally more used by the pharmacy profession than shared decision making. Concordance is the name given to the agreement between the

patient and the healthcare professional, reached after negotiation, that respects the beliefs and wishes of the patient in determining whether, when and how their medicine is taken (134,135). Although many consider concordance a shift from the old paternalistic compliance paradigm, concordance has also been criticised as being an ambivalent term and, at worst, simply window dressing (132,136,137). This criticism is related to the suggestion that concordance between healthcare professional and patient is the solution for the high societal and economic costs associated with non-compliance, and providing information is one of the pillars of concordance that can improve medicine taking (137). However, the goal of the healthcare professional should not be to persuade patients to take medication, but to make sure that the patient understands the consequences either way. Elwyn et al. clearly described four concordance tasks that should be completed before prescribing: elicit patient's views on the possibility of having to take medicine; explore those views with the patient; inform the patients of the pros and cons of taking and not taking medicine; and finally, involve the patients in the treatment decisions – over time and after reflection (80).

The concept of concordance may unavoidably lead to agreed decisions that are not what the healthcare professional thinks is best (136). We should accept that patients and physicians may not always agree. There will be times when the agreed decision may give the healthcare professional concerns, and leave them with a burden of responsibility. Nevertheless, the feeling is that at the end of the day the patient has to make the decision. In their recent long-term vision on the provision of medicines, the Dutch Ministry of Health, Welfare and Sport acknowledges a considerable responsibility of patients themselves for the way they use their medication (138). It is a role for healthcare professionals to ensure that in coming to that decision the patient is fully aware of the relative risks and benefits of the decision. Such negotiated decision making is believed to lead to more realistic and ultimately sustainable treatment decisions (139). On the other hand, there may be patients who insist on being prescribed a treatment for which there is no little evidence or benefit. As stated by Bond, concordance has to come to terms with these extreme situations to remain credible as a healthcare paradigm (136).
In the context of concordance, we should also recognise that many patients want to be involved in decision making, but not all (139,140). Some patients wish to make their own decisions, while others prefer to delegate decisions to professionals. Depressed patients seem to prefer a more active role in decision making compared with patients suffering from other chronic diseases (141). A key role for the professional is to assess the level of partnership the patients wants with respect to decision making. Even when patients do not want to take part in decision making, their views should be taken into account in the prescribing process. If

antidepressants are being considered, then asking patients about how they believe they work, what worries they have and the extent of the worries is important (37).
Concordance depends upon sharing balanced information. It has been found that healthcare professionals emphasise the benefits of treatment rather than discussing the possible harms, precautions or risks, and often accept smaller benefits from treatment than those being treated expect (49,90,142). In this respect, patients need different information, not more of the same, and more honesty about the uncertainties of medical knowledge is needed (137).

Patients can intend to adhere to a treatment decision with which they were involved and fully agree, and which takes into consideration all their concerns and wishes, but nevertheless find it difficult to keep to the prescribed regimen. In response to the experiences of medicine taking, patients' views on drug treatment and their need for information may change. Timing is important and information should be tailored to the patient's needs at that stage. In considering the decision whether to continue, patients constantly weigh the advantages and disadvantages of drug taking, as they perceive them. Therefore, it is essential to discuss the progress with treatment and elicit patients' considerations as to whether continue or discontinue treatment on an ongoing basis. During the first weeks of antidepressant treatment, patients require more intensive contact with healthcare professionals since side effects occur immediately while it takes some weeks before patients experience improvement. Once the initial side effects have subsided and patients experience a treatment response, contact may be less intensive but should be maintained. Patient's drug taking behaviour and the barriers to use should be discussed as a natural thing in the consultation between the healthcare professional and the patient, like other important aspects of illness and treatment.
In this context, and based upon our findings discussed previously, we would like to argue that there is a particular challenge for the pharmacy profession. For pharmacists, who dispense the prescriptions and have regular contact with the patient, there is an equally important role next to the prescribing physician to inform and counsel the patient. Moreover, they can play a key role in the evaluation of the patient's treatment pogress. Pharmacists have several obvious arguments to adopt an attitude of waiting in extending their supportive role towards patients. It is true that they are often not aware of the reasons for prescribing, and a more intensive interaction between pharmacist and patient will indeed come more naturally to some patients than to others. Nevertheless, pharmacists need to maximise their contribution in supporting patients during treatment. They have the intentions to widen their role, and should continue following this course.

Implications for research

Research should systematically incorporate patients' perspectives on medicines. Evaluation of patients' experienced advantages and disadvantages of drug taking may enrich quantitative research and may contribute to the understanding of why patients take certain decisions.

Observational research has revealed valuable quantitative information on antidepressant drug taking in daily practice. These studies have clearly shown that patients do not take their antidepressant medication as recommended by guidelines and advised by healthcare professionals. Quantitative research further aimed to identify sociodemographic characteristics that predict non-adherence or discontinuation of treatment. However, this approach was not very successful (115). Correlations between adherence and sociodemographic variables, while sometimes statistically significant, are generally quite modest in magnitude. Also, many interventional strategies have been tried, but results were disappointing whereas improved clinical outcome was restricted to those with major depressive disorder (72,82,143,144). Unfortunately, research failed to provide a sound understanding of the problem. Major reasons for the lack of progress lie in the missing understanding of the ways in which patients think and feel about their illness and treatment and the lack of insight into patients' experiences with treatment, and how these impact their behaviour. The current research approach often disregards that patients use antidepressants in a psychosocial environment, with beliefs about treatment, changing ideas about the self, social stigma, relationships, and life situations interacting to influence drug taking (3).

The basis of the research in this thesis is the course of drug taking, as consisting of three phases: initiation of drug treatment, execution of the drug regimen, and eventual, discontinuation. The use of this conceptual framework, originally suggested by Urquhart & Vrijens (145), has enabled us to unravel the key decisional events to understand why patients make certain decisions on certain points in time. The pluralistic approach, combining quantitative and qualitative research methods, has enabled us to go beyond databases evaluating the considerations and decisions regarding antidepressant drug taking from a patient perspective. We have used data from several sources that revealed new insights in the use of antidepressant medication in daily practice. Surveys among patients collecting medication at the pharmacy, experiences reported to a medicine reporting system, calls to a telephone information drug line, do all provide valuable information on patients' experiences, beliefs, needs and preferences regarding antidepressant treatment. Knowledge on

patients' perspectives on treatment has extended the findings from observational studies of treatment patterns and outcomes.
Obviously, despite the further understanding of patients' antidepressant drug taking behaviour, many issues remain unsolved. One of the major findings of our research is the influence of the illness severity and perception by patient and physician on the initiation and discontinuation of drug taking. Many patients receive prescriptions for less specific symptoms rather than depression or anxiety, which is associated with patients' decision to decline drug treatment. Recently, this phenomenon has also been described for inhaled corticosteroids (146). Further studies are needed to elucidate the role of patients' personal models of illness in the initiation and discontinuation of drug treatment, and to understand prescribing decisions of physicians and patient's role in this process. We believe this may contribute to the debate on the value of antidepressants in mild depression, especially in general practice.

There are several issues we did not address, but which need attention as well. For example, we did not explore underlying reasons for partial non-adherence in the execution phase of antidepressant drug taking and its relation with discontinuation of drug taking. Also, we focused on the first six months of treatment, and thus did not study patients' considerations and decisions on antidepressant drug taking over longer periods of time. Furthermore, our study mainly focused on patients treated with antidepressants in general practice. It is of importance to evaluate whether patients treated by psychiatrists differ in their considerations and decisions regarding antidepressant drug taking.
A final plea is for more research efforts on defining patient-centred outcomes. Adherence as an outcome measure is worthwhile in describing treatment patterns, but should not be used solely to judge patient care. We should focus on the meaning of adherence and its role in patients' health and quality of life (115). It is argued by Kravitz that there is a need for new measures that indicate not whether the patient does what the physicians says, but whether the patient performs behaviour that maximise his or her own personal utilities (147). Patients' perceptions of illness and symptoms, symptom burden, satisfaction with treatment, treatment needs and concerns, and treatment experiences are outcomes that can be further developed and implemented in research. In the Netherlands several reporting systems currently collect patient experiences with medicines, i.e. the spontaneous adverse drug reaction reporting system of the Netherlands Pharmacovigilance Centre Lareb and Lareb Intensive Monitoring (LIM) which both focus on drug safety, and Meldpunt Medicijnen initiated by DGV, The Dutch Institute for the Proper Use of Medicine, which accepts all type of drug experiences, including experiences on (in)effectiveness and practical problems. These systems each have their own merit.

However, developing a more systematic way, preferably on a longitudinal basis, for collecting and measuring patients' experiences might be of great value to evaluate medicines and understand patients' needs. Information and knowledge resulting from such a system should be made available to researchers, healthcare professionals and patients.

Final view

The research presented in this thesis has enriched the understanding of why patients take certain decisions regarding their antidepressant medication. Clearly, there appears to be room for improvement in patient care. We trust that our results find their way to physicians and pharmacists who treat and counsel the patients using antidepressant drugs in daily practice. Moreover, hopefully this thesis helps to motivate researchers to incorporate the patient perspective in their work. In the end, this will further improve the quality of patient care as well.

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Summary

Antidepressants have shown to be effective in the treatment of depression and anxiety by reducing symptoms, as well as the risk of relapse and recurrence. Yet, several obstacles have been acknowledged in the process of adequate diagnosis and treatment of patients with these diseases: underrecognition of the health problem by the patient, underconsultation among patients who need treatment, failure to recognise and diagnose the problem by the physician, failure to prescribe drug treatment for those who need so, and eventually, on the part of the patient, not taking the drug as instructed.
This thesis aims to understand why patients deviate from the prescribed and advised treatment with antidepressant drugs. The studies presented are build upon the framework of the course of drug taking consisting of three phases, namely initiation, execution and discontinuation of therapy. Up to now, little is known about patients' considerations on antidepressant drug taking, and how these relate to decisive moments in the course. In this thesis, we explore patients' considerations and decisions, based on the three phases within the course of taking antidepressants.

Chapter 2 addresses the initiation phase of antidepressant therapy. The initiation phase starts with the receipt of a prescription for a new course of treatment, followed by filling the prescription at the pharmacy and initiation of drug taking.
Initiation of antidepressant drug treatment has hardly been addressed in research. So far, no studies have focused on patients who recognise they have a problem, decide to consult their physician and receive an prescription, but don't initiate treatment. In Chapter 2.1 the incidence of patients who do not fill the first-time antidepressant prescription or fill only a single antidepressant prescription at the pharmacy was determined. Of all 965 patients receiving a first-time prescription for a second-generation antidepressant in general practice, 41 (4.2%) did not fill that prescription at the pharmacy and 229 (23.7%) filled only a single prescription of two weeks. Patients who consulted their general practitioner (GP) for a non-

specific indication, rather than for depression, anxiety, panic or obsessive compulsive disorder, were almost three times more likely (odds ratio (OR) 2.7; 95% confidence interval (CI) 1.8 to 3.9) to decline the first-time antidepressant prescription. Furthermore, the risk of declining treatment was almost five times higher (OR 4.9; 95% CI 2.1 to 11.3) in non-western immigrants, and almost two times higher (OR 1.8; 95% CI 1.2 to 2.8) in patients over 60 years of age.

In Chapter 2.2 characteristics of patients filling only a single prescription of a selective serotonin-reuptake inhibitor (SSRI) at the pharmacy were investigated, and reasons associated therewith were described. Filling only a single prescription was more common among patients with a low level of education (OR 2.6; 95% CI 1.1 to 5.9) and in patients who reported non-specific symptoms like fatigue, stress and restlessness as the reason for SSRI use (OR 2.7; 95% CI 1.4 to 5.5). Of the patients, 29.8% (n=17) did not start SSRI use, and 70.2% (n=40) discontinued SSRI use within two weeks. Fear of adverse effects and the actual occurrence of adverse effects were main reasons for this. Of the patients discontinuing treatment, 55.0% did so without informing their GPs.

Both studies showed that many patients accept a prescription from their treating physician, but do not accept and initiate the treatment plan. Illness severity, treatment needs and concerns revealed to be important factors.

To explore the role of drug information in the initiation of treatment, two further studies have been performed. Information is considered important in order to increase adherence, and is increasingly seen as a requisite to support patients' involvement in treatment decisions. Chapters 2.3 and 2.4 focused on patients' perceptions of the information received, patients' information needs, and the potential role of the pharmacy as provider of information.

Chapter 2.3 includes an interview study of 41 patients who recently started SSRI treatment, recruited through ten community pharmacies. The results showed that patients starting treatment with antidepressants feel they would benefit from information tailored to their personal needs. Many patients require more concrete and practical information on adverse effects and the delayed onset of action. In addition, explaining the term dependency in the context of SSRI use, discussing the necessity for use and the believed harms of long-term treatment is important for patients. However, information needs and the desired level of involvement vary largely between patients. Most patients perceive the role of the pharmacy in the provision of information as rather limited. They reported several barriers to an improved communication at the pharmacy, such as timing of information (which is mainly restricted to the first dispensing), lack of time and privacy, provision of information is protocolised rather than individualised, and inexperienced pharmacy staff.

The questionnaire study of 105 patients in Chapter 2.4 described how patients experience information on antidepressants given by the pharmacy at first prescription, and investigated whether verbal information additional to written information given at the pharmacy affects the duration of antidepressant use. The results showed a gap between patients' need for further information and discussing experiences on the one hand, and the limited role patients attribute to the pharmacy in antidepressant education and counselling on the other. Ninety percent of patients preferred to be informed by the prescribing physician. Only one quarter (26.7%) of patients stated that they received verbal information at first prescription at the pharmacy. Patients receiving verbal information along with written information did not use their antidepressant medication any longer than patients receiving written information only. Of the patients receiving written information only, 50.5% used their antidepressant longer than six months, while 46.4% of patients receiving both written and verbal information did so.
Overall, the studies in Chapter 2.3 and Chapter 2.4 showed that patients do not consider the pharmacy to be an important source of antidepressant drug information. Pharmacists could be more supportive in informing and counselling patients on antidepressant treatment. They need to recognise the differences between patients, and should tailor their communication style according to patients' preferences.

Chapter 3 focuses on the execution phase of antidepressant therapy. This phase refers to the events and issues surrounding the execution of the drug regimen itself.
Patients' health beliefs are important to consider in understanding why patients do not follow prescriptions for antidepressants. Eighteen community pharmacies participated in the observational study described in Chapter 3.1. We followed 110 patients until six months after presenting a first prescription for a second-generation antidepressant, prescribed by the GP. The study aimed to investigate whether health beliefs and health status assessed at the start of antidepressant treatment are associated with subsequent drug taking behaviour, and to explore how health beliefs and severity of illness develop over time. Of all patients, 8 (7.3%) did not initiate drug taking, 32 (29.1%) discontinued antidepressant use, 6 (5.5%) switched to different antidepressant medication, and 64 (58.2%) continued on the same antidepressant during follow-up. At inclusion, compared to the continuers, non-initiators had lower belief scores for impact of illness, perception of whether the GP thinks medication should be taken, intention to take medication, and attitude towards medication. Furthermore, non-initiators were less severely depressed. Discontinuers and continuers did not differ in depression and anxiety severity at inclusion. However, discontinuers more often reported less specific symptoms as reason for use, such as fatigue and sleeping problems. Compared to continuers,

switchers appeared to have higher illness severity scores at inclusion. During follow-up depression and anxiety severity improved for all treatment groups and reached the same level at six months. We concluded that health beliefs and illness severity influence patients' decisions about antidepressant drug taking. Patients' care can be improved by eliciting patients' beliefs about treatment and illness, and patients' perception of needing an antidepressant, before prescribing.

In order to explore experiences and beliefs of SSRI users in relation to initiation and execution of treatment, and to identify patterns of experiences and beliefs leading to discontinuation or continuation of treatment, Chapter 3.2 includes an in-depth interview study. Eighteen patients were interviewed three months after starting SSRI treatment prescribed by a GP, nine of whom had discontinued and nine continued. Considering similarities and disparities revealed two main patterns leading to either discontinuation or continuation of use. The disparities seemed to reach far beyond patients' health threat and the therapeutic effects of the drug. Rather, continuers were satisfied with the GP's role during initiation and execution of SSRI treatment, and fully trusted their decision. Continuers' attitude towards SSRI treatment was predominantly positive; they seemed to have little doubt about the necessity of using an SSRI, and hardly considered discontinuing for fear of relapse. Discontinuers, on the other hand, perceived the GP's role as limited, both during initiation and execution of SSRI treatment. They seemed to be less involved in decision making, and often appeared to have little confidence in their GP. Most discontinuers felt they lacked knowledge on SSRI use, and their attitude towards SSRI taking was rather negative. Discontinuers were often unconvinced about the necessity of using an SSRI, and appeared to have a strong desire to discontinue treatment. We concluded that discontinuation of SSRI treatment under current suboptimal circumstances is not favourable for patients. GPs and other healthcare professionals could be more supportive during the first months of SSRI treatment by eliciting patients' considerations for continuing or discontinuing treatment.

Reporting systems have shown to be a useful tool in collecting experiences and identifying issues related to the daily use of medicines. In Chapter 3.3 experiences related to antidepressant use reported by means of an internet-based medicine reporting system (www.meldpuntmedicijnen.nl) were studied. In addition, the nature of side effects reported by patients was compared with those reported by healthcare professionals. From May 2004 to May 2005, 2,232 individuals submitted a report to the internet-based medicine reporting system, 258 (12%) of whom submitted a report on antidepressants. Of these, 92 individuals (36%) reported on effectiveness, 40 (16%) of whom reported on ineffectiveness, and 217 (84%) submitted a report on side effects, with 202 (78%) reporting side effects that were experienced as negative. Fourteen individuals (5%) reported a practical issue and four reporters (2%) reported a reimbursement issue. Patients report the

ineffectiveness and side effects of antidepressant therapy as negative and leading to discontinuation of the therapy. Of all 630 side effects reported, 48% resulted in the patient discontinuing the antidepressant therapy; of these 29% did not inform their healthcare professionals. Of all the side effects reported, 52% were perceived as "very negative". Patients and healthcare professionals differ in the nature of the reported side effects. In comparison to the side effects reported by healthcare professionals, patients more often reported apathy, excessive sweating, ineffectiveness, somnolence, insomnia, sexual problems and weight increase. We suggest that patient experiences should be included in the evaluation of antidepressant treatment in clinical practice.

Chapter 4 addresses the discontinuation phase of antidepressant therapy. This phase refers to the causes and consequences of the termination of drug taking.
It is unclear whether patients perceive discontinuation of antidepressants as a problem. The study in Chapter 4.1 assessed whether concerns and problems experienced with drug discontinuation occur more frequently in patients using antidepressants than in patients using benzodiazepines, antipsychotics or non-psychiatric medication. Calls to a national telephone medicines information service (Geneesmiddel-Infolijn) received between 1990 and 2004 were examined using retrospective examination. Patients calling about antidepressants called about discontinuation three times as often (OR 2.8; 95% CI 2.6 to 3.0), and reported a problem with discontinuation five times more often (OR 5.4; 95% CI 4.6 to 6.3), compared to patients who called about non-psychiatric medicines. The proportion of questions about discontinuation and problems experienced with discontinuation was also higher in patients calling about benzodiazepines and antipsychotics, compared to patients calling about non-psychiatric medication. Discontinuation seems a general problem for all psychiatric medicines, and needs more attention in the communication between patients and healthcare professionals.
Tapering off antidepressant therapy, as opposed to abrupt discontinuation, has been recommended by several guidelines and in literature in order to diminish the occurrence of discontinuation symptoms. However, the evidence of a favourable effect of tapering is limited, and it is unclear how patients discontinue antidepressants in daily life. The study presented in Chapter 4.2 examined the way in which patients discontinue SSRI therapy in clinical practice and compared the effect of tapering with that of abrupt discontinuation on the occurrence of discontinuation symptoms. Of the 66 eligible patients ending SSRI therapy, 14 (21%) abruptly discontinued therapy. Abrupt discontinuation caused a significantly larger increase in the number of discontinuation symptoms (DESS events) than tapering (12.0 versus 5.9). A self-made tapering schedule was used by 28 (42%) patients, 20 (30%) used a GP-made schedule and 4 (6%) a tapering schedule made

by a psychiatrist. In addition, there was a tendency for an adverse effect of lack of knowledge of discontinuation symptoms at the start of therapy on the number of DESS events (8.9 versus 5.5).
We advise tapering SSRI therapy in clinical practice to prevent unnecessary adverse effects of discontinuation. Healthcare professionals need to inform patients on discontinuation issues early in the course and should be alert when patients need guidance on discontinuing therapy.

Chapter 5 provides a general discussion on the main findings of the research presented in this thesis. First, critical factors related to the initiation, execution and discontinuation phase of antidepressant therapy were discussed. We found illness perceptions and severity, treatment needs and concerns, and patients' views on information to be crucial in the initiation of antidepressant drug taking. Fundamental in exploring the execution phase of antidepressant therapy are changes in patients' attitude towards antidepressant treatment in response to the experiences while taking them. Furthermore, exploring the considerations that guide decisions to stop antidepressant drug taking, assessing whether patients taper treatment as opposed to abrupt discontinuation, and exploring the role of information in stopping treatment are important to understand patients' behaviour during discontinuation of antidepressant therapy.
Second, we considered our findings in the context of improving care for patients who start a new course of antidepressant therapy. We recommend that healthcare professionals should inform patients of the pros and cons of taking or not taking antidepressant medication, involve patients in the treatment decision, reflect progress with treatment over time, and elicit considerations as to whether continue or discontinue drug taking.
Finally, we presented our thoughts on the stimulation of research from a patient's perspective. We suggest research should systematically incorporate patients' perspectives on medicines. Evaluation of patients' experienced advantages and disadvantages of drug taking may contribute to the understanding of why patients take certain decisions.

Samenvatting

Antidepressiva zijn effectief bij de behandeling van angst en depressie, doordat ze zowel de klachten doen afnemen als de kans op terugval verminderen. In het proces van diagnose en behandeling van deze aandoeningen zijn diverse obstakels beschreven: patiënten zien hun klachten niet als een serieuze aandoening of gaan niet altijd met hun klachten naar een arts, artsen falen soms in het herkennen van de klachten of het diagnosticeren van de aandoening, in situaties waarvoor behandeling wenselijk is schrijven artsen niet altijd een geneesmiddel voor, en patiënten gebruiken het voorgeschreven geneesmiddel vaak anders dan geadviseerd.
Het doel van dit proefschrift is om beter te begrijpen waarom patiënten hun antidepressivum anders gebruiken dan artsen en apothekers voorschrijven of adviseren. Tot op heden is er weinig bekend over de overwegingen van patiënten rondom het gebruik van antidepressiva en welke overwegingen hierbij op beslissende momenten een rol spelen. De in dit proefschrift beschreven onderzoeken gaan uit van een proces van geneesmiddelgebruik dat bestaat uit drie fasen: starten, uitvoeren en stoppen van een behandeling. In dit proefschrift brengen we de overwegingen en beslissingen van patiënten in kaart op basis van de drie fasen in het proces van geneesmiddelgebruik.

Hoofdstuk 2 beschrijft de startfase van de behandeling met antidepressiva. Deze fase begint wanneer de patiënt een recept heeft gekregen voor een nieuwe behandeling, en omvat verder het ophalen van het geneesmiddel in de apotheek en het werkelijke starten met het gebruik van het geneesmiddel.
Het starten van een behandeling met antidepressiva heeft tot nu toe nauwelijks aandacht gekregen in onderzoek. Er zijn geen studies beschreven, waarin gekeken wordt naar patiënten die de stap genomen hebben om met hun klachten naar de arts te gaan en een antidepressivum voorgeschreven krijgen, maar vervolgens niet starten met het gebruik. In Hoofdstuk 2.1 worden patiënten in kaart gebracht, die een recept hebben gekregen voor een nieuwe behandeling met een antidepressivum

maar het geneesmiddel niet hebben opgehaald in de apotheek, en patiënten die slechts eenmalig een antidepressivum hebben opgehaald in de apotheek. Van de 965 patiënten, die van de huisarts een recept kregen voor een nieuwe behandeling met antidepressiva, haalden 41 (4,2%) het antidepressivum niet op in de apotheek en 229 (23,7%) kwamen slechts eenmaal naar de apotheek om een antidepressivum op te halen. De kans om de behandeling met antidepressiva af te wijzen was bijna driemaal zo hoog (odds ratio (OR) 2,7; 95% betrouwbaarheidsinterval (BI) 1,8 tot 3,9) bij patiënten die het antidepressivum kregen voor een niet-specifieke indicatie, dat wil zeggen een andere indicatie dan angst, depressie, een paniek- of een dwangstoornis. Bij mensen met een niet-westerse allochtone achtergrond was de kans om de behandeling met antidepressiva af te wijzen bijna vijfmaal zo hoog (OR 4,9; 95% BI 2,1 tot 11,3), en de kans was bijna tweemaal zo hoog (OR 1,8; 95% BI 1,2 tot 2,8) bij mensen ouder dan zestig jaar.

Het onderzoek in Hoofdstuk 2.2 beschrijft karakteristieken van patiënten die eenmalig een selectieve serotonine-heropnameremmer (SSRI) ophalen in de apotheek, en de redenen die zij hiervoor aangeven. SSRI's behoren tot de groep van antidepressiva, die specifiek de heropname van serotonine in de zenuwuiteinden remt, waardoor er meer serotonine beschikbaar komt. Serotonine is een chemische boodschapper die de informatieoverdracht tussen cellen in de hersenen verzorgt, en een rol speelt bij stemming en emoties. Het slechts eenmalig ophalen van een SSRI kwam vaker voor bij mensen met een lage opleiding (OR 2,6; 95% BI 1,1 tot 5,9), en bij mensen die niet-specifieke klachten noemden als reden voor gebruik (OR 2,7; 95% BI 1,4 tot 5,5). Van de onderzochte groep was 29,8% (n=17) niet gestart met het antidepressivum, en 70,2% (n=40) was wel begonnen, maar binnen twee weken weer gestopt. Angst voor bijwerkingen en het werkelijk optreden van bijwerkingen waren de belangrijkste redenen hiervoor. Van de mensen die waren gestopt, had 55% dit op eigen initiatief gedaan, zonder de huisarts hierover te informeren.

De eerste twee studies in dit proefschrift laten zien dat een groot aantal patiënten een recept voor een nieuwe behandeling met een antidepressivum aanneemt van de arts, maar de behandeling zelf niet accepteert en niet start met het gebruik ervan. De ernst van de klachten, de behoefte aan een behandeling met geneesmiddelen en zorgen over het antidepressivum spelen hierbij een belangrijke rol.

Om de rol van informatie in de startfase in kaart te brengen zijn twee andere onderzoeken uitgevoerd. Informatie wordt vaak gezien als oplossing om therapietrouw te verbeteren, en steeds vaker ook beschouwd als voorwaarde voor de patiënt om een overwogen beslissing te kunnen nemen over een behandeling. Hoofdstukken 2.3 en 2.4 richten zich op de perceptie van de patiënt op de ontvangen informatie, de behoefte aan informatie, en de rol van de apotheek bij het geven van informatie.

Hoofdstuk 2.3 beschrijft een onderzoek waarin 41 patiënten, recent gestart met een behandeling met SSRI's, zijn geïnterviewd. De patiënten waren benaderd via tien apotheken. De patiënten waren van mening dat de informatie beter afgestemd zou moeten worden op hun persoonlijke behoeften. Veel patiënten hebben behoefte aan concrete en praktische informatie over bijwerkingen en het vertraagd intreden van de werking. Uitleggen van het begrip afhankelijkheid in relatie tot het antidepressivum, onderbouwing van de noodzaak van gebruik, en de veronderstelde schadelijke gevolgen van langdurig gebruik, zijn belangrijke onderwerpen voor velen. Echter, de behoefte van patiënten aan specifieke informatie en de mate waarin patiënten mee willen beslissen over de behandeling verschilt sterk. De meeste patiënten beschouwen de huidige rol van de apotheek in de informatievoorziening als beperkt. Er worden verschillende factoren genoemd die een goede voorlichting in de weg staan: het moment van informatieverstrekking (meestal beperkt tot de eerste uitgifte), gebrek aan tijd en privacy, de informatie wordt niet op de persoon afgestemd maar gegeven volgens protocollen, en het personeel is niet altijd ervaren genoeg om de gewenste specifieke informatie te kunnen geven.
Hoofdstuk 2.4 beschrijft een onderzoek onder 105 patiënten, die een half jaar na de start van een antidepressivum een vragenlijst hebben ingevuld. Doel van het onderzoek was om te beschrijven hoe patiënten de informatie hebben ervaren, die zij kregen toen ze voor het eerst het antidepressivum ophaalden in de apotheek. Tevens wilden we onderzoeken of mondelinge informatie gegeven door de apotheek, naast schriftelijke informatie, invloed heeft op de duur van het gebruik van het antidepressivum. De resultaten laten een kloof zien tussen de behoefte aan informatie en het bespreken van ervaringen aan de ene kant, en de rol die patiënten hierbij zien voor de apotheek aan de andere kant. Patiënten zijn positief over de kwaliteit van de informatie die zij kregen toen ze de eerste keer het antidepressivum ophaalden. Echter, ze zien geen grote rol weggelegd voor de apotheek in de voorlichting over antidepressiva en het begeleiden van het gebruik. Negentig procent ontvangt de informatie over het antidepressivum het liefst van de huisarts. Slechts een kwart (26,7%) van de patiënten geeft aan ook mondelinge informatie te hebben gehad toen ze voor de eerste keer het antidepressivum ophaalden in de apotheek. Er was geen verschil in de duur van het gebruik tussen patiënten die aangaven alleen schriftelijke informatie te hebben gehad en degenen die zeiden ook mondelinge informatie te hebben gehad: respectievelijk 50,5% en 46,4% hebben het antidepressivum langer dan zes maanden gebruikt.
De onderzoeken in Hoofdstukken 2.3 en 2.4 laten zien dat de huidige rol van de apotheek als informatiebron wat betreft antidepressiva beperkt is. Apothekers kunnen meer ondersteuning bieden aan patiënten die antidepressiva gebruiken door het geven van voorlichting en begeleiden van het gebruik. Het is daarbij

belangrijk dat ze zich bewust zijn van de verschillen tussen patiënten, en dat ze hun manier van communiceren afstemmen op de voorkeuren van de patiënt.

Hoofdstuk 3 concentreert zich op de uitvoeringsfase van de behandeling met antidepressiva, met name op factoren en problemen rondom het gebruik zelf.
Overtuigingen en opvattingen van mensen met betrekking tot hun gezondheid zijn van belang om te begrijpen waarom patiënten hun geneesmiddel anders gebruiken dan voorgeschreven of geadviseerd. Achttien apotheken deden mee aan de observationele studie die beschreven wordt in Hoofdstuk 3.1. In deze studie zijn 110 patiënten gedurende zes maanden gevolgd vanaf het moment dat ze met een recept van de huisarts voor een nieuwe behandeling met een tweede-generatie antidepressivum in de apotheek zijn geweest. Het doel was om te onderzoeken of overtuigingen over de klachten en het geneesmiddel en de ernst van de klachten bij de start van de behandeling invloed hebben op de wijze waarop patiënten een antidepressivum gebruiken. Ook is hierbij onderzocht hoe overtuigingen en klachten zich ontwikkelen over de tijd. Van de deelnemende patiënten zijn er 8 (7,3%) niet gestart met het gebruik, 32 (29,1%) zijn gestopt met een antidepressivum, 6 (5,5%) zijn overgestapt naar een ander antidepressivum, en 64 (58,2%) hebben zes maanden lang hetzelfde antidepressivum gebruikt. Ten opzichte van de patiënten die hetzelfde antidepressivum zes maanden gebruikten, scoorden patiënten die niet gestart zijn met het gebruik lager op hun overtuigingen over de impact van de klachten, perceptie van de verwachting en mening van de huisarts, intentie om het middel te gebruiken, en attitude ten opzichte van het antidepressivum. Ook hadden de niet-starters minder depressieve klachten. Patiënten die gestopt zijn met het gebruik verschilden, wat betreft de ernst van de depressieve en angstklachten, niet van degenen die het gebruik van het antidepressivum continueerden. Echter, de stoppers noemden vaker niet-specifieke klachten als reden voor gebruik van het antidepressivum, zoals vermoeidheid en slaapproblemen (depressieve en angstklachten werden dus minder vaak genoemd). De patiënten die gedurende de zes maanden overstapten naar een ander antidepressivum hadden bij aanvang van de behandeling juist meer depressieve en angstklachten. Tijdens de vervolgperiode namen de depressieve en angstklachten in alle vier de groepen af, en na zes maanden was er geen verschil meer in de ernst van de klachten. Overtuigingen van patiënten over hun gezondheid en ernst van de klachten beïnvloeden de beslissing over het gebruik van het antidepressivum. We raden aan om de overtuigingen van patiënten, over hun klachten en het geneesmiddel, en de behoefte aan een antidepressivum in kaart te brengen alvorens een antidepressivum voor te schrijven.
Hoofdstuk 3.2 beschrijft een kwalitatief onderzoek, waarvoor diepte-interviews zijn gehouden met achttien patiënten, drie maanden na de start van een behandeling met SSRI's. Negen van hen waren inmiddels met het geneesmiddel

gestopt, de andere negen patiënten gebruikten de SSRI op dat moment nog. Doel van het onderzoek was om ervaringen en overtuigingen tijdens de start- en de uitvoeringsfase in kaart te brengen, en om patronen te identificeren die leiden tot stoppen of doorgaan van de behandeling. Het analyseren van overeenkomsten en verschillen van ervaringen en overtuigingen leverde twee duidelijke patronen op die leiden tot stoppen dan wel doorgaan van de behandeling. De verschillen tussen beide patronen gingen verder dan de impact van de klachten en de effecten van het antidepressivum. De gebruikers waren zeer tevreden over de rol van de huisarts, en vertrouwden volledig op de beslissing van de arts. Hun attitude ten opzichte van het antidepressivum was overwegend positief; ze twijfelden nauwelijks over de noodzaak om een SSRI te gebruiken. Omdat ze bang waren om terug te vallen in de oude situatie, dachten ze niet aan stoppen. De stoppers daarentegen vonden de begeleiding van de huisarts beperkt, zowel tijdens de start- als de uitvoeringsfase. Ze leken minder betrokken bij de beslissing om een antidepressivum te starten, en leken vaak weinig vertrouwen te hebben in de huisarts. De meeste stoppers vonden dat ze te weinig kennis hadden over het gebruik van het antidepressivum, en hun houding ten opzichte van de SSRI was vrij negatief. Vaak waren ze niet overtuigd van de noodzaak om een SSRI te gebruiken. Ze waren gestart met het middel maar hadden een sterke behoefte te stoppen met het gebruik ervan. We concludeerden dat patiënten stoppen met het gebruik van een SSRI onder omstandigheden die niet optimaal zijn, zonder voldoende ondersteuning. Dit beïnvloedt hun dagelijks leven negatief. Artsen en andere hulpverleners zouden patiënten meer kunnen ondersteunen in de eerste maanden van de behandeling. Het achterhalen van overwegingen van patiënten om te stoppen of door te gaan met het gebruik is hierbij essentieel.

Meldsystemen kunnen een belangrijke rol vervullen bij het verzamelen van ervaringen en identificeren van problemen gerelateerd aan het gebruik van medicijnen in de praktijk. Meldpunt Medicijnen is een digitaal meldpunt (www.meldpuntmedicijnen.nl), dat ervaringen verzamelt van medicijngebruikers. In Hoofdstuk 3.3 worden de ervaringen met antidepressiva die gemeld zijn tussen mei 2004 en mei 2005 nader onderzocht. Ook is de aard van de gemelde bijwerkingen vergeleken met de aard van de meldingen die artsen en apothekers in dezelfde periode deden bij het Nederlands Bijwerkingen Centrum Lareb. Van de 2232 personen die een melding deden bij het Meldpunt Medicijnen, meldden 258 (12%) over een antidepressivum. Hiervan meldden 92 (36%) personen over effectiviteit, 40 (16%) over ineffectiviteit, en 217 (84%) deden een melding over bijwerkingen. Veertien (5%) personen meldden een praktisch probleem en vier (2%) een vergoedingsprobleem. Per keer kunnen meerdere ervaringen gemeld worden. Ineffectiviteit en bijwerkingen van antidepressiva worden als negatief ervaren, en deze aspecten leiden er vaak toe dat mensen stoppen met het gebruik

van medicatie. Van alle 630 gemelde bijwerkingen, werd 52% als 'zeer negatief' ervaren, en 48% resulteerde in het stoppen van de behandeling. Het stoppen van het gebruik van het antidepressivum werd in 29% van de gevallen niet gemeld aan de arts of apotheker. Patiënten en professionals (artsen en apothekers) verschilden in de aard van de gemelde bijwerkingen. Patiënten meldden bijvoorbeeld eerder klachten als overmatig zweten, seksuele problemen, slaapproblemen en apathie. Artsen en apothekers meldden vaker zichtbare en meetbare klachten. Bij de beoordeling van het gebruik van antidepressiva in de klinische praktijk kunnen ervaringen van patiënten een belangrijke functie vervullen.

Hoofdstuk 4 richt zich op het stoppen van de behandeling met antidepressiva, waarbij met name de oorzaken en de gevolgen van het stoppen aan bod komen.
Er is weinig informatie over hoe mensen het gebruik van antidepressiva in de dagelijkse praktijk ervaren en het is onduidelijk of zijzelf het stoppen van het gebruik zien als een probleem. In Hoofdstuk 4.1 wordt onderzocht of vragen over het stoppen en problemen met het stoppen van het gebruik van geneesmiddelen vaker voorkomen bij patiënten die antidepressiva gebruiken dan bij gebruikers van benzodiazepinen, antipsychotica of niet-psychofarmaca. Alle gesprekken met de Geneesmiddel-Infolijn, die geregistreerd zijn vanaf de start van de infolijn in 1990 tot november 2004, werden bij dit onderzoek betrokken. De Geneesmiddel-Infolijn is een nationale telefonische geneesmiddeleninformatie service, geïnitieerd door de KNMP en een aantal consumentenorganisaties. Patiënten die belden over een antidepressivum belden driemaal zo vaak (OR 2,8; 95% BI 2,6 tot 3,0) en meldden vijfmaal zo vaak een probleem (OR 5,4; 95% CI 4,6 tot 6,3) dan mensen die belden over niet-psychofarmaca. Ook bij gebruikers van antipsychotica en benzodiazepinen was het aandeel van de gesprekken over stoppen en problemen met stoppen groter dan bij niet-psychofarmaca. Onze bevindingen laten zien dat mensen het stoppen met antidepressiva, maar ook stoppen met antipsychotica en benzodiazepinen, ervaren als een probleem. Stoppen lijkt een algemeen probleem voor psychofarmaca en zou meer aandacht moeten krijgen in de communicatie tussen patiënt en zorgverlener.
Richtlijnen adviseren om het gebruik van antidepressiva af te bouwen in plaats van abrupt te stoppen, om de kans op het optreden van onttrekkingsverschijnselen (ook wel ontwenningsverschijnselen genoemd) te verminderen. Het bewijs hiervoor is echter beperkt, en het is onduidelijk hoe patiënten in de dagelijkse praktijk het gebruik van hun antidepressivum stoppen. Het onderzoek in Hoofdstuk 4.2 beschrijft op welke manier mensen stoppen met het gebruik van SSRIs, en vergelijkt het effect van afbouwen met dat van abrupt stoppen op het optreden van onttrekkingsverschijnselen. Aan het onderzoek deden 66 patiënten mee die recent gestopt waren met hun SSRI; veertien (21%) van hen waren abrupt gestopt.

Er was een significant verschil in het aantal onttrekkingsverschijnselen (DESS-events) tussen abrupt stoppen en afbouwen van het gebruik (12,0 versus 5,9). Acht en twintig (42%) patiënten waren gestopt met een zelfgemaakt afbouwschema, twintig (30%) met een afbouwschema gemaakt door de huisarts, en vier (6%) met een schema gemaakt door de psychiater. Er was een trend in het verschil tussen het aantal onttrekkingsverschijnselen bij mensen die wél en die niet op de hoogte waren van het mogelijk optreden ervan (8,9 versus 5,5). Afbouwen van SSRI gebruik is gewenst om onnodig optreden van onttrekkingsverschijnselen te voorkomen. Professionals zouden patiënten in een vroeg stadium kunnen adviseren over stoppen en alert zijn wanneer patiënten begeleiding bij stoppen nodig hebben.

In Hoofdstuk 5 plaatsen we de belangrijkste bevindingen van dit proefschrift in een breder perspectief. Allereerst bespreken we de factoren die een cruciale rol spelen in de drie fasen van het proces van geneesmiddelgebruik. De ernst van de klachten en de perceptie van de patiënt op de klachten, behoefte aan een behandeling met een geneesmiddel, de zorgen over het antidepressivum, én de behoefte van de patiënt aan informatie en begeleiding zijn belangrijk om het gedrag van de patiënt in de startfase te begrijpen. Essentieel in de uitvoeringsfase van de behandeling zijn de veranderingen in de attitude van de patiënt ten opzichte van het antidepressivum door de ervaren werking en bijwerkingen. Het in kaart brengen van de overwegingen die kunnen leiden tot stoppen en invloed hebben op de manier van stoppen (afbouwen of abrupt stoppen), en de rol van informatie en begeleiding bij het stoppen zijn van grote betekenis bij het begrijpen van het gedrag rondom het stoppen van de behandeling.
Daarna gaan we in op de betekenis van onze bevindingen voor de zorg van patiënten die starten met een behandeling met antidepressiva. We adviseren professionals om patiënten te informeren over de voor- en nadelen van een behandeling met antidepressiva, maar ook te bespreken wat de gevolgen kunnen zijn wanneer besloten wordt om geen behandeling te starten. Daarbij raden we aan de patiënt actief te betrekken in de beslissing om een behandeling met een antidepressivum te starten. De positieve en negatieve effecten van de behandeling zouden regelmatig geëvalueerd moeten worden, waarbij de overwegingen van de patiënt om door te gaan dan wel te stoppen besproken kunnen worden.
Tot slot geven we onze visie op het stimuleren van onderzoek vanuit het perspectief van de patiënt: de gebruiker van het geneesmiddel. De mening en opvattingen van patiënten over het gebruik van geneesmiddelen zouden op een meer systmatische manier geïntegreerd kunnen worden in onderzoek. Inzicht in de door de patiënt ervaren voor- en nadelen van het gebruik van geneesmiddelen is essentieel om te begrijpen waarom patiënten bepaalde beslissingen nemen

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Apotheek Van der Mooren	Aalsmeer
Kring-apotheek Abcoude	Abcoude
Apotheek Archipel	Almere
Apotheek Jansen	Amersfoort
Apotheek Keyser	Amersfoort
Apotheek Nieuwland	Amersfoort
Kring-apotheek Kattenbroek	Amersfoort
Service Apotheek Soesterkwartier	Amersfoort
Apotheek Bankras	Amstelveen
Apotheek Dr. F. Amelink	Amstelveen
Apotheek Westwijk	Amstelveen
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LLOYDS Apotheek Amstelveen Middenwaard	Amstelveen
Rembrandt Apotheek	Amstelveen
Schiphol Apotheek BV	Amstelveen
Apotheek Confuciusplein	Amsterdam
Apotheek Koning	Amsterdam
Apotheek W.H. van der Meulen	Amsterdam
Kring-apotheek Nieuw Sloten	Amsterdam
Kring-apotheek Plesman	Amsterdam
LLOYDS Apotheek De Buitenveldert	Amsterdam
Molukken Apotheek	Amsterdam
Apotheek Kisters Ascherman	Arnhem

Kring-apotheek West Maas en Waal	Beneden-Leeuwen
Service Apotheek Rochus	Boxmeer
Apotheek Breukelen	Breukelen
Kring-apotheek Ambix	Bunschoten
Kring-apotheek FLeiR Apotheek Veldhuizen	De Meern
Mediq Apotheek De Meern	De Meern
Apotheek Havinga	Den Haag
Bohemenwijk Apotheek	Den Haag
Waldeck Apotheek	Den Haag
Kring-apotheek Veldhuizen	Ede
Apotheek de Greiden	Heerenveen
Kring-apotheek Swarte	Heerenveen
Linde Apotheek	Heerenveen
Schoterpoort Apotheek	Heerenveen
Apotheek Hoek van Holland	Hoek van Holland
Kring-apotheek Vreugdenhil	Hoogland
Kring-apotheek Het Oude Dorp	Houten
Apotheek Go	IJsselstein
Apotheek Lamberts	IJsselstein
Mediq Apotheek IJsselveld	IJsselstein
Apotheek Van Hulten	Joure
s-Gravelandse Apotheek	Kortenhoef
Apotheek Stevenshof	Leiden
Kring-Apotheek Boomstede	Maarssenbroek
LLOYDS Apotheek Made	Made
Apotheek de Batau	Nieuwegein
Apotheek Fokkesteeg	Nieuwegein
Apotheek Overlander	Purmerend
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Apotheek van der Laan	Rotterdam
Apotheek Zevenkamp	Rotterdam
Service Apotheek Ramleh	Rotterdam
Wilgen Apotheek	Rotterdam
Apotheek Nieuwland	Schiedam
Apotheek Hoogland	Sliedrecht
Thorbecke Apotheek	Sliedrecht
Escura Apotheek Wolverlei	Soest
Mediq Apotheek Overhees	Soest
Mediq Apotheek Soest	Soest

Mediq Apotheek Soestdijk	Soest
Mediq Apotheek Jan Heijns	Tilburg
Mediq Apotheek JulianaStaete	Tilburg
Mediq Apotheek Schouwburgring	Tilburg
Escura Apotheek Boogaard	Uithoorn
Apotheek D.G. Boswijk	Utrecht
Apotheek Koert	Utrecht
Apotheek Lunetten	Utrecht
Apotheek Marco Polo	Utrecht
Apotheek Oog in Al	Utrecht
Apotheek Overkapel	Utrecht
Apotheek Pluymakers	Utrecht
Kring-apotheek Lusse	Utrecht
Kring-apotheek Overvecht	Utrecht
Kring-apotheek Van Keule	Utrecht
Kring-apotheek Wilhelmina	Utrecht
Lombok Apotheek	Utrecht
LLOYDS Apotheek De Panter	Voorburg
Mediq Apotheek Vorden	Vorden
Apotheek Romijn	Zaandam
LLOYDS Apotheek Zeewolde	Zeewolde
Kring-apotheek Hoge Dennen-Kerckebosch	Zeist
Mediq Apotheek De Brink	Zutphen
Escura Apotheek De Ringvaart	Zwanenburg

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Curriculum Vitae

Katja van Geffen was born in Eindhoven, the Netherlands, on September 3, 1962. She graduated in 1980 at the Maaslandcollege in Oss. In 1988, she obtained her Master's degree at the Utrecht University, and in 1989 she became a pharmacist. She joined Glaxo, now GlaxoSmithKline, in 1990. She started as a Clinical Research Associate on studies in the respiratory area, and was appointed as head of the Respiratory Department in 1994. Since 1999, she has been working as the head of the Science Shop for Medicines of the Department of Pharmaceutical Sciences of Utrecht University. In addition, from 2004 to 2008 she has also worked part-time at the Division of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences of Utrecht University on the studies described in this thesis. In January 2008, the Science Shop merged with UPPER (Utrecht Pharmacy Panel for Education and Research) of the Department of Pharmaceutical Sciences. The new organisation UPPER is part of Kennispunt Bètawetenschappen of the Faculty of Science, and aims to further bridge the gap between science, pharmacy practice and society.