

PATIENTS REPORTING OF SUSPECTED ADVERSE REACTIONS TO ANTIDEPRESSANTS. A PILOT METHODOLOGICAL STUDY.

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Abstract

The benefits and the disadvantages of patient reporting have been much debated in the last years. In spite of being considered 'anecdotal', patient reporting had overcome at last the prejudices among regulators and it is now allowed in many Western countries. Moreover, studies have demonstrated that patient reporting is a useful tool for collecting experiences and information about what is a 'tolerable' adverse effect, but also about the daily use of medicines.

The current study aims to develop a systematic method that enables patients to report experienced adverse events that they think are due to their medication, using questionnaires returned in prepaid envelopes. Antidepressant agents were the drugs chosen for this pilot study. We also wanted to determine the feasibility of a community pharmacy-based system to inform the patients about the possibility to report adverse events.

Patients in our study were willing to report adverse events. The patients proved to be capable of identifying and providing a clear description of their experiences that were due to antidepressant use. Antidepressant adverse effects represent a burden for the patients, being probably underestimated by the healthcare professionals.

Rezumat

Beneficiile și dezavantajele raportării reacțiilor adverse direct de către pacienți au fost mult dezbătute în ultimii ani. În ciuda faptului că au fost considerate „anecdote”, raportarea de către pacienți a depășit prejudecățile întâmpinate în rândul autorităților ce reglementează activitatea de farmacovigilență și este permisă acum în numeroase țări. Studiile efectuate au demonstrat faptul că raportarea direct de către pacienți este o metodă eficientă de colectare a informației referitoare la experiențele acestora legate de administrarea medicamentelor și a ceea ce înseamnă un efect advers „tolerabil”.

Prezentul studiu are ca obiectiv dezvoltarea unei metode sistematice care să permită pacienților să raporteze evenimentele adverse experimentate, utilizând chestionare. Medicamentele antidepressive au fost cele alese pentru acest studiu pilot. Am dorit de asemenea să determinăm fezabilitatea unui sistem care se bazează pe farmaciile comunitare pentru a informa pacienții despre posibilitatea raportării evenimentelor adverse.

Pacienții din cadrul acestui studiu au fost dornici să raporteze evenimentele adverse pe care le consideră asociate cu terapia urmată. Aceștia au demonstrat că sunt perfect capabili să recunoască și să ofere informații și descrieri clare ale evenimentelor adverse experimentate și să pună în balanță atât riscurile cât și beneficiile unei terapii.

Keywords: patients reporting, adverse effects, antidepressants

Introduction

A recent development in the field of pharmacovigilance was the recognition of the patient as an important player [1]. Patients are the ultimate goal of the healthcare systems. They are the ones that benefit from drugs, but also the ones that experience the adverse drug effects.

The current pharmacovigilance system relies on reporting of adverse drug reactions (ADRs) mainly from healthcare professionals. Although many solutions have been proposed for increasing the number of ADRs reports, underreporting is still the main problem affecting the spontaneous reporting systems worldwide [2].

After much debate about the usefulness of patients direct reporting, without physicians or pharmacists acting as intermediary, many countries now accept reports directly from patients. The expressed concerns about the usefulness of the patients' reports regarded the quality and the accuracy of the information provided by the patients in order to contribute to signal generation. Van Grootheest and colleagues argued that "the quality of the report concerns the information given in the report. Some minimum elements are needed in order to make a report useful". They stated that physician and patient reports do not differ when it comes to quality [3, 4]. With respect to the accuracy of these reports, patients appear to be capable of correctly discriminating probable adverse drug reactions from other adverse clinical events [5]. On the other hand, drug safety is much more than signal generation. The main concern of pharmacovigilance is the early detection of new, unlabelled ADRs, but in the context of drug safety, pharmacovigilance systems are also intended to record the frequency of ADRs occurrence, evaluate factors that may increase the risk for developing an ADR, and provide information to prescribers with the goal of preventing ADRs [5].

A recent review of published literature on patients reporting of suspected adverse drug reactions concluded that it has more potential benefits than drawbacks [5]. Patients can provide first-hand information about their experiences with drugs - including over-the-counter drugs or complementary medication – of whose administration the doctor may not be informed. The patients can also provide information on adverse changes in the quality of life, which can be very important and bothersome for them and which can lead to non-adherence to a prescribed treatment. Because of their lack of medical knowledge, patients might report associations that may seem unlikely from a medical point of view, but may turn out to be a true signal. One of the main drawbacks of the unfiltered information from patients' reports is the lack of medical confirmation which may interfere with the evaluation of the ADR.

Even despite this, De Langen and colleagues concluded, after three years of experience with patients reporting in the Netherlands, that “patient reporting in spontaneous reporting systems is feasible and it contributes significantly to a reliable pharmacovigilance” [6].

In Romania, according to the current legislation, patients are allowed to report adverse drug reactions directly to the National Pharmacovigilance Center inside the National Drug Agency [7], but patients are not informed about this possibility, neither encouraged to report. This is not surprising, as a recent study about physicians’ attitude towards voluntary reporting of adverse drug reactions demonstrated that up to 68% of the physicians interviewed were not informed about the existence of a national spontaneous reporting system [8].

As few studies on ADR reporting involved patients directly, we looked for an approach that allowed patients to share their experience of using medicines. The present study was developed in order to enable patients to report symptoms that they believe to be due to an antidepressant prescribed drug, using closed and open alternative questionnaires. The antidepressant agents chosen for this pilot study as evidence for consumers reporting in the developed world showed a high rate of reports on the adverse events of this medication [5, 9].

As community pharmacies were successfully used in the past by other investigators for the purpose of pharmacovigilance, patients were informed and recruited for the study when they filled up the prescription for one of the six antidepressants studied (fluoxetine, paroxetine, sertraline, citalopram, escitalopram and venlafaxine) [10]. We also intended to see if such a system for patients reporting encouraged by pharmacists is feasible in everyday practice.

Materials and methods

Twelve community pharmacies in Cluj-Napoca were asked to collaborate for this study. Patients that came with a prescription for one of the six antidepressants were informed that “a survey of any suspected unpleasant event following the antidepressant administration” allows them to report adverse events. They were given no other advice, but the pharmacists were asked to mention that the information they will provide for this survey will be strictly confidential. For the patients that consented to participate in this survey, the pharmacists made a note of the name and telephone number of all participants and of the drug and the doses prescribed. No later than two weeks after the patients’ visit to the pharmacy, the patients were phoned by one of the investigators offering

complementary information about the study and were asked for the address where the questionnaire on adverse events with the prepaid envelope could be sent. As the completed forms were returned anonymously, no evidence about the patients that returned the questionnaires could be kept and so no reminder telephone calls were made.

The questionnaires were developed using previously published work [9, 11]. The questionnaires asked for information regarding the antidepressant, the dose and the indication it was prescribed for, concurrent other therapy and other diseases. Regarding the adverse reactions, there were open and closed questions (check-box). The adverse reactions with check-box were the ones that are usually more frequently reported for the antidepressants in the study and they were grouped into organ-system classes (neurological, psychiatric, gastrointestinal, cardiac and general adverse events) [9]. The patients were also asked about the adverse events that bother them most, the severity of these events (as in mild, moderate, severe and very severe) and about the reporting of these events to their physicians. The adverse events reported were classified into 'probable', 'possible' and 'unlikely' adverse drug reactions, based on causal relationship between the event and the antidepressant drug, taking into account the concomitant other medication and diseases. This system of classification was proposed by Jarernsiripornkul and colleagues [11].

Results and discussion

In total 85 patients agreed to participate to the study. Although we maintained an active collaboration with the participating pharmacists, reminding them constantly about the importance and potential benefits of this system, few patients were informed about the possibility to report adverse events. On the other side, the ones that were informed might have refused the participation, as patients with depression can be reluctant to talk about their condition and report adverse reactions in a survey. Enduring encouragement is needed to stimulate pharmacy personnel to include patients who come with the prescription for the drug under investigation in such a system.

After the investigators phoned the 85 patients, offering complementary information, all of them further agreed to participate to the study. So a total of 85 postal questionnaires were sent. Fifty questionnaires (59%) were returned completed. This response rate is a good one compared with similar studies that obtained overall responses rates of 40% [10, 11]. It is though lower than the 77% response rate that was achieved in a study where reminder telephone calls were made, but reminder calls can be

impractical in a larger survey [10]. Response rate differed among the drugs, being greatest for citalopram, although the actual number was small (n=3), and for escitalopram (Table I).

Table I
Response rate and adverse events reported for each antidepressant

Drug	Number of sent questionnaires	Number of returned questionnaires (%)	Total number of adverse events reported (median; range)
Paroxetine	33	14 (42.4)	118 (8.4; 1-21)
Sertraline	11	5 (45.4)	39 (7.8; 5-11)
Fluoxetine	8	5 (62.5)	42 (8.4; 2-19)
Escitalopram	22	17 (77.2)	108 (6.3; 1-16)
Citalopram	3	3 (100)	14 (4.6; 1-10)
Venlafaxine	8	6 (75)	54 (9.3; 2-26)

The majority of the respondents were female (68%). The average age of the patients taking antidepressants was 45.8 years (range 20-82). Most of the patients were taking antidepressants for depression disorder (n=26), out of which 5 for major depression and 8 for depression associated with anxiety; the others were taking them for panic disorder (n=18) and bipolar disorder (4).

More than half of the responders claimed to have other concomitant pathology out of which the diseases of the musculoskeletal system (n=17), followed by the ones of the circulatory (n=15) and nervous system (n=10) and mental and behavioral disorders (n=8) were the most frequent. The use of other drugs was reported by 74% of the responders, who claimed to be taking 1 to 8 prescribed drugs. The psycholeptic drugs were the most frequently used (especially the benzodiazepines, buspirone, olanzapine and quetiapine), followed by antiepileptics and psychoanaleptics. The cardiovascular agents were also used by a high number of patients.

Number and nature of reported adverse events (AE)

All the patients that returned the questionnaires reported at least one adverse event that they associated with the use of the antidepressant drug. The total number of reported adverse events was 375, and the median per patient was 7.5 (range 1-26). Patients receiving paroxetine and escitalopram, the most numerous, reported a wider range of adverse events. More than half of the patients (54%) reported more than 5 adverse events. Table II shows the organs and systems mostly affected by these adverse events.

Table II
Reported adverse events grouped by system/ organ

System/ Organ	Number of reported adverse events (AE) (%*)						Total (%)**
	Paroxetine	Sertraline	Fluoxetine	Escitalopram	Citalopram	Venlafaxine	
Nervous	26 (22.03)	8 (20.5)	9 (21.4)	26 (24)	3 (21.4)	13 (24.1)	85 (22.6)
Mental	33 (27.9)	11 (28.2)	9 (21.4)	22 (20)	4 (28.6)	6 (11.1)	85 (22.6)
Digestive	17 (14.4)	4 (10.2)	8 (19)	11 (10.2)	1 (7.1)	10 (18.5)	51 (13.6)
Skin	1 (0.8)	1 (2.5)	1 (2.4)	7 (6.5)	0	0	10 (2.6)
Cardiac	10 (8.4)	3 (7.7)	3 (7.2)	5 (4.6)	1 (7.1)	3 (5.6)	25 (6.7)
General	31 (26.2)	12 (30.7)	12 (28.6)	37 (34.3)	5 (35.7)	22 (40.7)	119 (31.7)
Total	118	39	42	108	14	54	375

* The value represents the percent of AE out of the total number of AE reported for that antidepressant;
 ** The value represents the percent of AE out of the total of reported AE

Patients were evidently willing to report adverse events that they thought to be associated with the administration of the antidepressant, the general adverse events (e.g. fatigue, somnolence, excessive sweating weight gain, sexual disorders) being the ones commonly reported. It has already been emphasized that self-reports can be a useful source of information on minor adverse drug reactions which are bothersome and important to the patients and may lead to non-adherence to a prescribed treatment [9]. Adverse events that affected the nervous and the mental systems were also frequently reported. Table III presents the most common reported adverse events.

Table III
Most common reported adverse events and patients' characteristics

Adverse event	No. of reports	Female (%)	Median age (range)
Headache	15	60	42.6 (21-67)
Dizziness	16	69	44 (22-82)
Somnolence	18	66.6	41.4 (21-75)
Fatigue	18	55.5	45.8 (21-82)
Tremor	10	70	45.1 (21-82)
Paresthesia	14	50	38.3 (21-56)
Anxiety	12	33.3	38 (21-56)

Table III (continued)
Most common reported adverse events and patients' characteristics

Adverse event	No. of reports	Female (%)	Median age (range)
Confusion	8	37.5	36 (21-56)
Sleep disorder	10	60	42.4 (21-75)
Nightmares	9	89	46.2 (31-64)
Insomnia	8	37.5	41.75 (21-52)
Amnesia	10	80	47 (31-56)
Difficulty in concentrating	19	63.1	43.1 (21-75)
Suicidal thoughts	5	60	41.6 (21-54)
Excessive sweating	19	79	47.5 (22-82)
Xerostomia	20	65	47 (21-70)
Weight gain	17	64.7	44.4 (22-75)
Increased appetite	18	77.7	42.1 (20-82)
Sexual disorders	31	70.9	38.8 (20-67)

It is clear that patients tend to report adverse reactions that are less visible to healthcare professionals (HCPs). These adverse reactions usually go underreported by HCPs due to the differences of perception of what a serious, or severe adverse reaction is. In a study that compared the reports of the healthcare professionals with the patients' reports, the adverse reactions to antidepressants reported by the HCPs were rashes, laboratory abnormalities, muscle and joint complaints, extrapyramidal and congenital disorders [9].

In the present study, adverse events like confusion, difficulty in concentrating, headache, somnolence, insomnia or other sleep disorders were reported by patients younger than the medium age. All these events represent a problem as they directly affect the everyday life of these patients and their capacity to work. Although the healthcare professionals are aware of these antidepressants adverse effects, their burden and their frequency is definitely underestimated by the physicians.

Regarding the adverse events that bothered the patients, the most frequent indicated ones were somnolence, dizziness, headache, weight gain, excessive transpiration and sexual disorders. The severity of these symptoms was appreciated as being mild by a total number of 13 patients, moderate by 15 patients and severe by 12 patients. Ten patients did not answer this question. The symptoms that were considered severe by the patients were aggression and suicidal thoughts, headache, confusion,

amnesia and difficulty in concentrating. Up to 30% of the patients indicated that they had reported all their adverse events to their physicians.

Fifty-four percent of the total number of the reported adverse events was classified as being probable caused by the antidepressant, with a further of 45% classified as being possible and only 1% as being unlikely. Although it was emphasized that adverse events checklist could increase the reporting rates through suggestion, patients on antidepressant drugs are likely to report symptoms that are indeed adverse reactions [11].

Conclusions

The proposed method enables the identification of adverse reactions that though are considered well-known, are bothersome to the patients. However, if further improvements of this system can be implemented, it could be used as a feasible system to identify and characterize also new adverse reactions of medicines, as patients seemed willing and capable of providing clear description of their experiences and of balancing the benefits and the burden of a particular therapy.

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