UNIVERSITE DE LAUSANNE – FACULTE DE BIOLOGIE ET DE MEDECINE

DEPARTEMENT UNIVERSITAIRE DE PSYCHIATRIE

OFF-LABEL UTILIZATION OF ANTIDEPRESSANTS

THESE

préparée sous la direction du
Professeur honoraire Pierre Baumann
et avec la collaboration du Dr méd. Daniele Fabio Zullino, MER, Hôpital Universitaire de Genève

et présentée à la

Faculté de biologie et de médecine
de l'Université de Lausanne
pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Bruno SCHWARTZ

Médecin diplômé de la Confédération Suisse

Originaire de Meyrin (Genève)

LAUSANNE
2008

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Rapport de synthèse

Utilisation « off-label » de médicaments antidépresseurs
(OFF-LABEL UTILIZATION OF ANTIDEPRESSANTS)

De nombreuses études sont effectuées sur les antidépresseurs avant leur mise sur le marché, puis des règles précises sont établies pour leur prescription dans des indications délimitées. Leur utilisation dans des indications « off-label » (hors indication officiellement admise) manque souvent de validation par des bases de données scientifiques et leur prescription se base le plus souvent sur un consensus proposé par des experts. Le but du présent travail a été d'étudier les habitudes de prescription de psychiatres d'hôpitaux en ce qui concerne les antidépresseurs, en comparant des patients traités pour une dépression et des troubles anxieux avec des patients recevant un traitement « off-label ».

Pour cette étude, les données d'utilisation de médicaments sont celles recueillies lors de 6 jours de référence, entre avril 1999 et novembre 2001, à l'hôpital psychiatrique de Lausanne (Suisse) comprenant 98 lits. La prescription de médicaments chez 174 patients a été prise en compte.

Tandis que le diagnostic n'influençait pas le choix entre des nouveaux et anciens antidépresseurs, les patients présentant un trouble anxieux avaient un risque 4.5 fois ($p < 0.05$) plus élevé et les patients présentant un autre diagnostic 8 fois plus élevé de recevoir une comédication antipsychotique, en comparaison avec des patients dont le diagnostic primaire était un trouble dépressif. De plus, les patients recevant comme comédication un hypnotique non-benzodiazépine avaient moins de risque que l'on prescrive un ancien antidépresseur ($p < 0.05$). Alors que les patients avec un trouble anxieux et ceux souffrant d'une dépression majeure recevaient un antidépresseur à des doses comparables, les patients répondant à une indication off-label étaient de préférence traités avec des doses plus faibles.

Les résultats de cette étude suggèrent que les psychiatres d'hôpitaux développent des préférences en ce qui concerne le choix de la classe d'antidépresseurs, et qu'ils les utilisent alors aussi bien dans des indications reconnues que non-reconnues. Puis ils semblent adapter la dose et la comédication en tenant compte du diagnostic, ce qui confirme l'hypothèse initiale de l'étude.

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OFF-LABEL UTILIZATION OF ANTIDEPRESSANTS

Daniele Fabio Zullino[1a], Bruno Schwartz[2a], Romain Bilancioni[3], Pierre Baumann[3]

University Hospitals of Geneva, Switzerland: Division of Substance Abuse[1], Private Practice, Geneva, Switzerland[2], University Department of Adult Psychiatry, Clinical Research Unit, Prilly-Lausanne, Switzerland[3]

[a] The contribution of these authors has to be considered equivalent

Summary: While antidepressant prescription rules are established for approved indications by large-scale studies, off-label utilization naturally often lacks the validation by large scientific databases, and is at its best based on expert consensus. The aim of the present survey was to study the prescription habits of hospital psychiatrists with regard to antidepressants, comparing patients treated for depressions and anxiety disorder with patients receiving off-label antidepressant treatment.

Methods

Data on drug use for this study were based on 6 reference days from April 1999 to November 2001 in the 98-bed psychiatric hospital of the University of Lausanne, Switzerland. The drug prescriptions of 174 patients were assessed.

Results

Whereas the diagnosis did not influence the choice between newer or older antidepressants, patients presenting an anxiety disorder were 4.5 times more likely ($p<0.05$) and patients with other diagnoses 8 times more likely ($p<0.001$) to receive an antipsychotic comedication compared to patients whose primary diagnosis was a depressive disorder. Also, patients receiving concomitantly a nonbenzodiazepine hypnotic were less likely to be prescribed an older antidepressant ($p<0.05$). While patients with anxiety disorder and those with major depression received their antidepressants at comparable doses, patients with an off-label indication were treated preferentially with lower doses.

Conclusions

The results of this survey suggest, that the prescribing hospital psychiatrists developed preferences with regard to the choice of the antidepressant class, which they then used for both registered and off-label indications. They then seemed to adapt the dose and the comedication according to the diagnosis, confirming the initial study hypothesis.

Key words: *Antidepressants; Prescription habits; Off-label use; Depression; Anxiety disorders*

Introduction

The analysis of factors which influence the prescription of psychotropic drugs, and especially antidepressants, has repeatedly been the subject of recent research (2, 4). Prescription habits have been shown to be especially influenced by characteristics of the regional health care system, physician management style, physician specialty and training, public attitudes, drug cost and availability, patient preferences, local tradition, education, marketing and formulary (5, 7, 8, 13, 19). Conversely, prescribing physicians seem to take less into account patient characteristics (5, 8).

A major source of concern of many drug utilization studies has been the appropriateness of psychotropic drug prescribing practices, pointing out the frequent lack of concordance between psychiatric diagnoses and prescribed psychotropic medications (4, 8, 18).

While tricyclic antidepressants were rapidly used for other indications after their introduction, this broadening of indications has been even more of an issue for the newer generation antidepressants. Many of the newer drugs can presently be considered valid alternatives, especially in the treatment of anxiety disorders (3) and eating disorders (10). Their popularity for the treatment of depressive symptoms in patients with somatic comorbidities is also largely due to their enhanced safety profiles, relative to those observed in older drugs (15). The broad range of diagnoses for which antidepressants are prescribed has recently been pointed out in some drug utilization surveys, where up to 40 % of patients receiving an antidepressant were not diagnosed with depression (14, 16).

While guidelines for the use of antidepressant medications have been established for approved indications by several large-scale studies, the off-label utilization naturally often lacks this validation, and is at most based on expert consensus.

Whereas differences between patients treated with antidepressants for approved indications and those with off-label prescriptions have been found with regard to the intended treatment duration (16),

showing shorter treatment duration for off-label utilization, data comparing other aspects of antidepressant treatment, such as doses, comedications etc., is still lacking.

The aim of the present survey is to study the prescription habits of hospital psychiatrists with regard to antidepressants, comparing patients treated for depression and anxiety disorder with patients receiving off-label antidepressant treatment, examining particularly the administered doses and comedications. The underlying hypothesis was that physicians would choose the same class of antidepressants in off-label indications as they would for approved indications, but that they would adjust doses and comedication in response to the clinical situation.

Methods

The present study was developed as part of the AMSP project (Arzneimittelsicherheit in der Psychiatrie = drug safety in psychiatry), which is a program for continuous assessment of adverse drug reactions in psychiatric inpatients under naturalistic conditions of routine clinical treatment. The methodology has been described elsewhere (6, 21, 23, 24). Currently, more than 35 German, Swiss, Austrian, Hungarian and Belgian sites are participating. Data on drug use in the participating hospitals are based on two reference days per year. All drugs given on a reference day are recorded along with age, sex, and diagnosis (ICD-10) for all patients under surveillance. The daily dosage is also recorded.

Data of the present study were drawn out of 6 reference days from April 1999 to November 2001 in the 98-bed psychiatric hospital of the University of Lausanne, Switzerland. Currently, the mean hospitalization duration is 14 days and the nurse/bed ratio is 0.95.

Definition of drug classes

Antidepressants were classified into tricyclic drugs (TCA) and drugs of the newer generations (DNG). DNGs were defined as the selective serotonin re-uptake inhibitors paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine as well as mirtazapine, reboxetine, nefazodone and moclobemide. The class of TCAs included the tricyclic compounds clomipramine, trimipramine, imipramine, amitriptyline and dibenzepin.

To analyze the effect of prescribing patterns of sedating vs nonsedating antidepressants and concomitant antipsychotic medication or benzodiazepines, the antidepressant group was divided into sedating (SA) versus nonsedative drugs (NSA). The sedative compounds were: trimipramine, clomipramine, nefazodone, and mirtazapine.

Benzodiazepines were classified as one group, including sedative and hypnotic drugs, as sedative benzodiazepines were often also used as hypnotics, the different indications therefore being difficult to assess. Nonbenzodiazepine hypnotics (NH) formed a further drug class, including zolpidem, zopiclone and zaleplon.

Dose ranges

In order to compare the antidepressant prescription with regard to applied doses, three dose ranges were defined for each administered drug (Table 1). For patients receiving more than one antidepressant, the doses were summed up: twice the low dose range giving a middle dose range, a low dose and a middle dose or two middle doses giving a high dose.

Label and off-label indications

Based on the primary diagnosis, patients were grouped into 3 classes: (1) Depression, (2) Anxiety Disorder, and (3) Other Disorders.
As no patient had a manic or mixed episode as primary diagnosis, all patients presenting an ICD-10 diagnosis of affective disorder were depressive.
Whereas all used antidepressants are approved in Switzerland for depression, they differ with regard to the approval for the different anxiety disorders. Anxiety disorders were nevertheless grouped into one class, as knowledge of the diverse approved indications among the prescribing physicians could not be assumed. On the other hand, physicians are locally trained to consider newer antidepressants as the first line pharmacotherapy for anxiety disorders.

Analyses

In descriptive data analyses means and standard deviations were calculated for numerical variables while nominal ones frequency categories values and percentages are reported. In exploratory analyses, the differences between groups were tested with chi-square tests (for nominal variables) and analyses of variance for numerical ones.

Predictive models were built with multivariate logistic regression analysis. Binary stepwise logistic regression analysis was used to determine factors predicting the prescription of older antidepressants, of antipsychotics, of benzodiazepines and nonbenzodiazepine hypnotics. A further model predicting the antidepressant dose range, used was analyzed by multinominal stepwise logistic regression. Multinominal logistic regression broke the regression up into a series of binary regressions comparing each group to a baseline group, which we determined to be the low dose range group. The backward Wald method was applied.

The data were analyzed using the SPSS for Windows program, version 12.0.

Results

Characteristics of the sample

The drug prescriptions of 174 patients were assessed. The mean age was 42.6 ± 11.6 (range 20 - 66) and the proportion of women 59.2 %. There were no differences between index days with regard to age and sex distribution.

The distribution regarding the primary ICD-10 diagnosis was: Mental and behavioral disorders due to psychoactive substance use (F10): 10 (5.7 %); Schizophrenia, schizotypal and delusional disorders (F20): 47 (27.0 %); Mood disorders (F30): 81 (46.6 %); Neurotic, stress-related and somatoform disorders (F40): 10 (5.7 %); Behavioral syndromes associated with physiological disturbances and physical factors (F50): 1 (0.6 %); Disorders of adult personality and behavior (F60): 25 (14.4 %).

Number of prescribed drugs per patient and comedications

The mean number of drugs administered was 4.3 ± 1.7 (range 1 – 10). Forty-eight patients received nonbenzodiazepine hypnotics (27.6 %), 138 (79.3 %) had benzodiazepines prescribed, 25 (14.0 %) received conventional antipsychotics, 61 (35 %) atypical antipsychotics, 22 (12.6 %) anticonvulsants, 13 (7.5 %) lithium, and 104 (59.8 %) somatic drugs. There was no secular effect with regard to the number of prescribed drugs and comedications when comparing the prescriptions of 1999, 2000 and 2001.

Type of antidepressants

Among the investigated patients, 102 (58.6 %) were treated with SSRIs, 18 (10.3 %) patients received venlafaxine, 22 (12.6 %) received mirtazapine, 29 (16.7 %) had a tricyclic antidepressant (TCAs), and 16 (9.2 %) received another drug. Thirteen patients (7.5 %) were treated simultaneously with two antidepressants

Impact of patients characteristics on antidepressant prescription

The prescription of the different types of antidepressants for patients with depression, anxiety disorder and others are shown in Tab. 2.

The proportion of patients receiving TCA were 16/81 (19.8 %) for depressive patients, 2/10 (20 %) for patients presenting an anxiety disorder, and 11/83 (13.3 %) among the patients with another disorder (Chi-square 1.322; n.s.).

Table 3 shows the result of the stepwise logistic regression, with the choice of an older antidepressant being the dependent variable and the index year, the diagnostic class, sex, age and the prescription of concomitant drugs (benzodiazepines, nonbenzodiazepine hypnotics, anticonvulsants, lithium, somatic drugs) as independent parameters. With increasing age the probability of receiving an older antidepressant increased ($p<0.05$). Furthermore, a clear secular trend appeared, as the probability of receiving an older antidepressant was significantly lower in 2000 ($p<0.05$) and in 2001 ($p<0.05$) compared with 1999. Also, patients receiving concomitantly a nonbenzodiazepine hypnotic were less

likely to be prescribed an older antidepressant (p<0.05). The diagnostic class was not retained as a predictive parameter. The positive predictive value of the model was 85.1%.

Prescription of concomitant antipsychotic drugs

The correspondent result of the stepwise logistic regression analysis is shown in Tab. 4. The following parameters were entered: Index year, sex, age, diagnostic class, antidepressant type (older vs. newer) and concomitant treatments. Only the diagnostic class was retained, patients with anxiety disorder or other non-depressive disorders presenting significantly higher odds-ratios compared to patients with the diagnosis of depression. The positive predictive value of the definitive model was 73.0 %.

Prescription of concomitant benzodiazepines

A stepwise logistic regression predicting the prescription of benzodiazepines including the following parameters was computed: Sex, index year, age, diagnostic class, antidepressant type (older vs. newer and sedative vs. non-sedative), and concomitant treatments. None of the parameters was retained.

Prescription of concomitant nonbenzodiazepine hypnotics

The following parameters were used to compute the corresponding stepwise logistic regression (Tab. 5): Sex, index year, age, diagnostic class, antidepressant type (older vs. newer and sedative vs. non-sedative), and concomitant treatments. Only the parameter comparing older vs. newer antidepressants was retained. Patients receiving an older antidepressant had a lower probability of receiving a concomitant nonbenzodiazepine hypnotic (p<0.05). The positive predictive value of the retained model was 72.4 %.

Dose range

The distribution with regard to the prescribed doses was: Low dose 48 patients (27.6 %), medium dose 96 (55.2 %) and high dose 30 (17.2 %). The multinominal stepwise logistic regression analysis was computed with the following parameters: Sex, diagnostic class, antidepressant class (newer vs.

older), and prescription of antipsychotics, benzodiazepines, nonbenzodiazepine hypnotics, anticonvulsants, lithium or somatic drugs (Tab. 6). The group of individuals having received the antidepressant medication at a low dose range were defined as the reference group. The parameters of the diagnostic class and of the antidepressant class were retained. Whereas patients with anxiety disorder did not differ from those with depressive disorder with regard to the applied doses, those with other diagnoses received less often medium (p<0.001) and higher (p<0.001) antidepressant doses. Furthermore, those receiving an older antidepressant had an odds ratio of 6.66 to receive their antidepressant treatment rather at a high than at low dose, compared to the patients having a treatment with newer antidepressants only (p<0.01).

Discussion

The aim of the present study was to investigate if hospital psychiatrists would prescribe antidepressants and comedication differently for patients with a registered indication compared to those administered antidepressants on an off-label basis.

Whereas the diagnosis did not seem to influence the choice of a newer or and older antidepressant, it was significantly associated with the prescription of antipsychotic comedication and antidepressant dose. Patients presenting an anxiety disorder were 4.5 times more likely and patients with other diagnoses 8 times more likely to receive an antipsychotic comedication compared to patients whose primary diagnosis was a depressive disorder. While patients with anxiety disorder and those with major depression received their antidepressants at comparable doses, patients with an off-label indication were treated preferentially with lower doses.

While antipsychotics, on one hand, high potency as well as low potency, have often been advocated as being valid alternatives to benzodiazepines as anxiolytic treatments, and, on the other hand, sedative antidepressants have been suggested to reduce the need of concomitant benzodiazepine use, our data did not confirm these assumptions. Neither the use of sedative antidepressants, nor the

prescription of benzodiazepines had an impact on the prescription of concomitant antipsychotics. Antipsychotics were only prescribed in the function of the diagnosis.

A secular trend was found with regard to the prescription of tricyclic antidepressants, these older drugs being less likely to be prescribed in 2000 and 2001 compared to 1999, even when Checking for confounding factors like diagnosis or comedication. As the prescription of a nonbenzodiazepine hypnotic was associated with a lowered odds of receiving an older antidepressant, one could hypothesize that the observed secular trend may be due to the replacement of tricyclics used for their sedative or sleep-enhancing properties by nonbenzodiazepine hypnotics.

As in previous studies investigating prescription habits of psychotropic drugs (1, 9, 11, 12, 17), polypharmacy was highly prevalent, the mean number of prescribed drugs being 4 with a range from 1 to 10 drugs per patient. Whereas polypharmacy has long been considered a malpractice in earlier studies, it has become increasingly apparent nowadays that psychiatric polypharmacy can have some advantages, i.e., to further improve sleep, have a more potent anxiolytic or sedative effect and to overcome therapy resistances (17, 20, 22).

One further intriguing finding was the observation that the risk of receiving a tricyclic antidepressant augmented with increasing age. This is at first sight counter-intuitive, as the risk of cardiovascular and other side effects may be more important in elder patients and should have discouraged the doctors from prescribing these drugs for those patients. On the other hand, elder patients may be often the more chronic patients and may have received the antidepressant for longer habitual treatment, which the physician could possibly not have had the courage to change anymore. As the present data are only collected on a crossover basis, this assumption can, however, not be tested out.

The results of this study need to be viewed against their methodological limitations. The method of index day assessments allows only cross sectional analyses for each patient. The course of the prescription, i.e., titration schemes, and the duration of the antidepressant treatment as well as of the comedications cannot be evaluated. That not every patient can be considered as having been already stabilized on the medication at the index day, especially data on doses, but also all other data, has to

be interpreted with caution. Also, diagnoses were not based on a structured interview, which may have diminished their validity. However, as the ICD-10 diagnoses were derived post hoc from the medical records, they surely better reflect clinical practice. Furthermore, only the first diagnosis (hospitalization indication) was retained.

The two reference days were always fixed for the period of late spring and late autumn, allowing each center to choose a day within ± 7 days. The choice of seasonally fixed reference days may be a confounding factor in depressive disorders as well as anxiety disorders.

With regard to generalizability, one has to consider that the survey was limited to one site only, the hospital being University based and organized in specialized wards. The refuse, biases by local customs and conditions of practice cannot be excluded.

In conclusion, the present results thus suggest that the prescribing hospital psychiatrists developed preferences with regard to the choice of antidepressant class, which they then used for both registered and off-label indications. They then seemed to adjust the dose and the comedication according to the diagnosis, confirming the initial study hypothesis.
Factors influencing this spreading out of prescription habits from labeled to off-label indications remain to be explored. The results furthermore generate various related important questions, which should be addressed through further research: Does the rapid spreading out of off-label prescription increase or decrease the risk of adverse drug reactions? Does it unduly increase or decrease costs? What is the impact of doctors' interaction with pharmaceutical companies?

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Corresponding author:

Dr. Daniele Zullino, Service d'abus de substances, Hôpitaux Universitaires de Genève
Rue Verte 2, 1205 Genève, Switzerland, e-mail: daniele.zullino@hcuge.ch

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Tab. 1:
Dose ranges (in mg/d) of antidepressants prescribed in this study

	Low	Medium	High
Citalopram	<40	40 - 60	>60
Fluoxetine	<40	40 - 60	>60
Paroxetine	<40	40 - 60	>60
Fluvoxamine	<100	100 - 200	>200
Sertraline	<100	100 - 200	>200
Venlafaxine	<150	150 - 300	>300
Nefazodone	<200	200 - 400	>400
Reboxetine	<4	4 - 8	>8
Mirtazapine	<30	30 - 60	>60
Trimipramine	<100	100 - 200	>200
Clomipramine	<150	150 - 300	>300
Imipramine	<150	150 - 300	>300
Amitriptyline	<150	150 - 300	>300
Dibenzepin	<160	160 - 360	>360
Moclobemide	<300	300 - 600	>600

Tab. 2:

Diagnostic class and type of prescribed antidepressant

	Depression		Anxiety Disorder		Others	
	n	**%**	**n**	**%**	**n**	**%**
SSRI	34	42.0	8	80.0	51	61.4
venlafaxine	11	13.6	0	0.0	4	4.8
mirtazapine	12	14.8	0	0.0	8	9.6
tca	6	7.4	1	10.0	0	12.0
others	7	8.6	0	0.0	9	10.8
combination	11	13.6	1	10.0	1	1.2

Tab. 3:
Stepwise logistic regression model for use of older antidepressants

	OR[a]	95% Confidence Intervals	p
Age	1.05	1.01 - 1.09	0.015
Index year			
1999			0.011
2000	0.24	0.08 - 0.72	0.011
2001	0.29	0.10 - 0.84	0.022
Nonbenzodiazepine hypnotic	0.25	0.07 - 0.92	0.037

[a] Odds ration for the probability of receiving an older antidepressant

Tab. 4:

Stepwise logistic regression model for use of concomitant antipsychotic drugs

	OR[a]	95% Confidence Intervals	p
Diagnostic class			
Depression	1		<0,001
Anxiety	4.51	1.13 - 17.94	0.033
Other	8.59	4.19 - 17.60	<0,001

[a] Odds ration for the probability of receiving a concomitant antipsychotic drug

Tab. 5:

Stepwise logistic regression model for use of concomitant nonbenzodiazepine hypnotic

	OR	95% Confidence Intervals[a]	p
Prescription of an older antidepressant	0.26	0.07 - 0.89	0.032

[a] Odds ration for the probability of receiving a concomitant nonbenzodiazepine hypnotic

Tab. 6:

Logistic regression model for choice of antipsychotic dose range

		Medium dosis			High dosis		
		OR	p	95% Confidence Intervals	OR	p	95% Confidence Intervals
Diagnostic class							
	Depression						
	Anxiety	0.98	0.988	0,10-9,35	2.21	0.514	0,21-23,83
	Other	0.21	<0,001	0,09-0,48	0.08	<0,001	0,03-0,27
Prescription of an older antidepressant		1.11	0.865	0,34-3,56	6.66	0.004	1,82-24,29