

Pharmacovigilance of Neuroleptics and Benzodiazepines in the Psychiatric Teaching Hospital of Benin Republic

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Abstract

Background: Data on adverse drug reactions (ADRs) related to neuroleptics and benzodiazepines in sub-Saharan Africa psychiatry setting are few indicating the need for psychotropic drugs safety surveillance in clinical care.

Objective: To determine profile of the drugs prescribed, incidence, type and risk factors associated with adverse drug reactions (ADRs) among patients on neuroleptics and benzodiazepines.

Methods: Patients initiated on neuroleptics and/or benzodiazepines between March 2014 and September 2014 were evaluated in a prospective cohort analysis. Prospective study of active pharmacovigilance during six months was performed. Each patient was followed for two months. The French method was used to determine the causality assessment.

Results: 86 inpatients or outpatients were enrolled. 65.12% experienced a side event (SE). Among them, 22.09% had insomnia, 17.44%, drowsiness; 5.81%, dyskinesia; 4.65%, an appetite increase and 4.65%, headaches. The percentages of patients with 1, 2, 3, 4 and 5 side events were 39.28%, 41.07%, 8.92%, 7.14% and 3.57% of the 65.12% respectively. The average number of side events per patient was similar in hospitalized patients and in those treated ambulatory (1.97 vs. 1.92). The causality assessment of the side events to the drugs prescribed to each patient is predominantly doubtful (52.29%). It is likely in 44.95%, very likely in only 1.83% of the cases and plausible in 0.92% of the patients. All SEs occurred during the first month, most during the first week. The management of adverse drugs reactions led to drug doses reduction only in 23% of the cases while responsible drugs were stopped in 5.77% of the cases.

Conclusion: The relatively high frequency of typical antipsychotics of use and low daily dose of benzodiazepine among our patients merit further investigation and systematic efficacy and safety monitoring. Typical antipsychotics should be made more available and monotherapies should be encouraged. The pharmacovigilance should be developed in the country by installing a National Center and by training health professionals.

Keywords: Adverse drugs reactions; Neuroleptics; Benzodiazepine; Benin; Pharmacovigilance

Introduction

The World Health Organization (WHO) defines health as: "A state of complete physical, mental and social wellbeing and not just an absence of disease or infirmity." Mental health is the ability to deal with normal stress situations of life, to work productively and contribute to community wellbeing. Conversely, psychiatric disorders hinder everyday life with emotional, cognitive, interpersonal and behavioral repercussions.

About 450 million people suffer from mental or behavioral troubles in the world [1] and 33% of the total incapacity years are imputable to neuropsychiatric problems. A study by Wittchen et al. in 2011 in the European Union (EU), Switzerland, Iceland and Norway, revealed that 38% of the population of the UE has a trouble of the psyche once a year [2]. In Morocco, a 2005 study on 5, 498 persons over 15, established the percentage of people with a recurrent disorder at 48.9%, that of severe depression at 26.5% and that general anxiety at 9.3% [3]. In Benin Republic, a 2013 study on a sample of 1, 530 people found the prevalence of schizophrenia to be 1.1% [4].

Psychotropic drugs are used to manage psychiatric troubles in combination with other means such as psychotherapy and social rehabilitation. Psychiatric diseases are marked by biochemical alterations in the brain and the drugs used against them act either on the concentration of the neurotransmitters of the synaptic cleft or on

their ability to bind to receptors [5] affecting directly brain functioning and producing undesirable changes in behavior. According to their action, psychotropic drugs are distinguished as psycholeptiques (hypnotics, narcoleptics), psychoanaleptics (antidepressors) and psychodysleptics (which induce toxicomania) [6]. Polymedication is frequent in psychiatry which can increase the risk of adverse effects or drug interactions [7] the most prescribed categories of drugs being psychotropics such as neuroleptics and benzodiazepines (21.4%-France and 15.5%-Spain) [8]. Moreover, rare clinical trials of psychotropics are conducted in sub-Saharan Africa and patients are selected according to stringent criteria and comorbid medical conditions are usually excluded. Furthermore, there is a paper written on clinical trials, mostly those in psychiatry indicates that ADRs are not always constantly reported [9] and there is an issue showing that

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an appropriate data might be distorted in some cases [10]. This implies good phase IV studies to ensure patients' safety particularly among African patients.

Pharmacovigilance has been defined by the World Health Organization (WHO) as the science and activities related to the detection, assessment, understanding and prevention of adverse drug effects [11]. In Benin Republic, Pharmacovigilance is still in an embryonary state [12]. No published data exists on the pharmacovigilance of psychotropic drugs including neuroleptics and benzodiazepines. This is the reason behind this first report of adverse drug reactions.

Methods

It is an observational and prospective study conducted at the National Psychiatry University Hospital of Cotonou in Benin from March to September 2014 including 18 year old or older patients, hospitalized or ambulatory followed up and under neuroleptics and/or benzodiazepines. The variables studied were the type and moment of side events, the clinical outcome of treatment, age, sex, religion, ethnicity, marital status, profession and level of study, number of drugs prescribed, therapeutic observance, polymedication and comorbidity.

The data was collected during one on one consultation or over the phone using a predetermined questionnaire. Data entry was done using the following software: Microsoft Office Excel 2007 version and Epi Data 3.1. Data analysis consisted in the description of the variables and the study of possible relations among qualitative variables on the one hand and between the qualitative variables on the other hand. Chi-square and Student's exact tests have been used to look for possible relations between the variables. A logistic multivariate regression analysis with the version 11.0 of the Stata software was utilized to look for factors linked to the side events. A 5% significance threshold has been adopted. The study has been accepted by the Committee on Ethics and Research of Applied Biomedical Sciences (CER-ISBA N°41 du 03/07/2014). The enlightened consents of patients or of their relatives were received and the data collected was treated confidentially with respect of anonymity.

Results

Age

17.44% of the patients belonged to the age group (18-24) and 2.33% to the age group (65-70). The most represented age group was (25-34) with 34.88% of the patients as shown by Table 1.

Sex

The sex ratio (W/M) of the patients was 1.1 (52.33% of women).

Probable diagnoses

Patients' pathologies are dominated by chronic psychoses as one can see in Table 2. Comorbidity was present in 11.63% of the case. The other diseases were high blood pressure (5.8%), diabetes (2.3%), asthma, HIV infection and epilepsy (1.16% each). The medical histories recorded showed that 22% of the patients were taking psychoactive drugs; 12.79%, tobacco, 12.79% alcohol; 4.65%, cannabis; and 2.33% coffee. Some patients were taking several of these substances.

Profile of the drugs prescribed

Chlorpromazine, Haloperidol, Trihexyphenidyle, Amitriptyline

and Diazepam were the most prescribed drugs in the department. Table 3 shows all the drugs prescribed with their pharmacological classes and doses and (Figure 1) indicates that the most prescribed neuroleptics were the first generation ones: Chlorpromazine and Haloperidol (42.22% for each). Diazepam was the main benzodiazepine used. The average dose in milligrams is obtained by dividing all doses prescribed during a day by the number of patients put under a particular medication.

Age	Number	Frequency in %
18 -24	15	17.44
25-34	30	34.88
35-44	14	16.28
45-54	19	22.09
55-64	6	6.98
65-70	2	2.33
Total	86	100

Table 1: Patients' age.

Pathologies	Ambulatory	Hospitalization	Total
Chronic psychosis	13	11	24
Depression	19	1	20
Acute psychosis	7	11	18
Polytoxicomania	2	4	6
Bipolar disorder	2	2	4
Pharmacopsychosis	3	0	3
Others	4	7	11
Total	50	36	86

Table 2: Pathologies diagnosed.

DCI	Class	Dose (mg)
Alimemazine (n*=1)	Antihistaminics	7.5
Alprazolam (n=8)	Benzodiazepines	0.78
Amitriptyline (n=29)	Antidepressors	42.67
Bromazepam (n=3)	Benzodiazepines	6
Captopril (n=1)	Antihypertensives	50
Carbamazepine (n=17)	Antiepileptics	658.82
Chlorpromazine (n=57)	Neuroleptics	107.89
Clomipramine (n=1)	Antidepressors	25
Clonazepam (n=1)	Benzodiazepines	2
Cyamemazine (n=1)	Neuroleptics	50
Diazepam (n=27)	Benzodiazepines	13.33
Enalapril + nitrendipine (n=1)	Antihypertensives	10
Haloperidol (n=57)	Neuroleptics	8.86
Heptaminol (n=1)	Vasodilators	375.6
Hydroxyzine (n=4)	Antihistaminics	53.13
Levomepromazine (n=6)	Neuroleptics	91.67
Lorazepam (n=7)	Benzodiazepines	3.75
Oxazepam (n=10)	Benzodiazepines	49
Paracetamol (n=1)	Analgesics	2000
Prazepam (n=2)	Benzodiazepines	37.5
Promethazine (n=17)	Antihistaminics	72.06
Risperidone (n=12)	Neuroleptics	5
Tianeptine (n=3)	Antidepressors	25
Tiapride (n=2)	Neuroleptics	110
Trihexyphenidyle (n=40)	Antiparkinsonians	5
Tropatepine (n=5)	Antiparkinsonians	10
Zolpidem (n=7)	Hypnotics	8

Table 3: Profile of the drugs prescribed.

Number of drugs prescribed per patient

Hospitalized patients received more drugs including more neuroleptics than those treated ambulatory, but the number of benzodiazepines has been the same (Table 4 and Table 5).

Observance and side events

91.86% of the patients took their medicines correctly. Nevertheless, 65.12% of all patients had at least one side event. The percentages of patients with 1, 2, 3, 4 and 5 side events were 39.28%, 41.07%, 8.92%, 7.14% and 3.57% of the 65.12% respectively. The average number of side events per patient was similar in hospitalized patients and in those treated ambulatory (1.97 vs. 1.92). A total of 109 SEs was recorded, mainly sleep disturbances (insomnia: 22.09% and day sleeping: 17.44%). Table 6 displays the types and frequencies of the SEs. The causality assessment of the side events to the drugs prescribed to each patient is predominantly doubtful (52.29%). It is likely in 44.95% of the cases, very likely in only 1.83% of the cases and plausible in 0.92% of the patients. There has been no case in which the side events were incompatible with the treatment. Table 7 specifies the side events related to drug-drug interactions and their types (PD or PK), while Table 8 indicates the time-to-event and shows its shortness (mostly during the first week and always during the first month).

Discussion

Adverse drug reactions characteristics and profiles among black African psychiatry patients are lacking. To our knowledge, it is first study reporting adverse drug reactions actively in psychiatry patients in west Africa. The size of the study population authorizes the recording

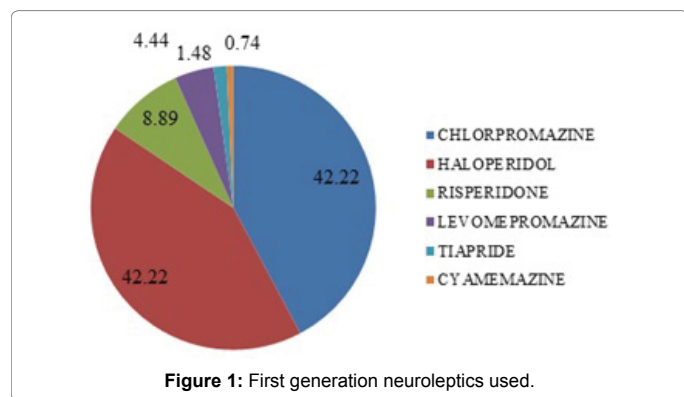


Figure 1: First generation neuroleptics used.

Factor	All drugs	Neuroleptics	Benzodiazepines
Mean	3.73	1.57	0.76
Standard deviation	0.12	0.07	0.07
Median	4	3	2
Mode	4	2 et 4	1
Minimum	1	1	1
Maximum	7	5	3

Table 4: Number of drugs per patient.

	Ambulatory (n=50)		Hospitalized (n=36)		p-value
	Average	SD	Average	SD	
All drugs	3.54	0.13	4	0.21	0.06
Neuroleptics	1.38	0.1	1.83	0.09	0.002
Benzodiazepines	0.72	0.09	0.8	0.11	0.55

Table 5: Number of neuroleptics and benzodiazepines per in and outpatient.

Events	Number	Frequency in %
Insomnia	19	22.09
Day sleeping	15	17.44
Headache	8	9.3
Fever	6	6.98
Agitation	5	5.81
Asthenia	5	5.81
Better appetite	4	4.65
Vertigo	4	4.65
Diarrhoea	3	3.49
Abdominal pain	3	3.49
Acute dyskinesia	3	3.49
High blood pressure	3	3.49
Agressiviness	2	2.33
Falls	2	2.33
Chills	2	2.33
Orthostatic hypotension	2	2.33
Dry mouth	2	2.33
Vomiting	2	2.33
Anorexia	1	1.16
Muscle cramps	1	1.16
Pain in the eye	1	1.16
Dyspnoea	1	1.16
Night hypersialorrhoea	1	1.16
Hypoglycemia	1	1.16
Arterial hypotension	1	1.16
Urinary incontinence	1	1.16
Instability	1	1.16
Muscle stiffness	1	1.16
Stereotypy of gestures	1	1.16
Extrapyramidal symptoms	1	1.16
Tachycardia	1	1.16
Ocular twitch	1	1.16
Stiff neck	1	1.16
Trembling of the hands	1	1.16
Coca cola urines	1	1.16
Nettle rash	1	1.16
Swollen face	1	1.16

Table 6: Types and frequencies of the side events.

of the most frequent side events. In contrary to other studies that followed only hospitalized patients [13,14] or ambulatory ones [15,16]. This study included both types of patients allowing a global view of the SEs' profile. The French method had been used to perform causality assessment because it helps collect data of good quality though its specificity is not the best compared to Naranjo et al., Jones's and WHO's.

As in other studies, acute and chronic psychoses were predominant (61.11%). Though there are better neuroleptics, the second generation ones, the most prescribed neuroleptics to the study population are Chlorpromazine and Haloperidol, probably because of their lower cost. Interestingly, the average dose of Chlorpromazine (107.89 mg/patient/day) is four to seven times inferior to the one (401 à 800 mg/day) recommended by a study in 2008 for optimal efficacy with few side events [17]. Janicak et al. suggested 300 mg to 600 mg [18]. Three reasons could explain the low dose of Chlorpromazine found in this study: the association with other psychotropic drugs, the recent character of the diagnoses and the higher sensitivity of the black African people to neuroleptics. On the other hand, the average dose of Haloperidol in

Interactions	Side events	Type of interaction
Chlorpromazine+carbamazepine	Arterial	Pharmacodynamic
	Hypotension	Pharmacocinetic
Chlorpromazine+haloperidol	Better appetite	PD
	Stereotypy of gestures	PD
	Ocular twitch	PD
	Trembling of the hands	PD
	Neck stiffness	PD
Chlorpromazine+haloperidol+amitriptyline+trihexyphelidyle	Dry mouth	PD
Chlorpromazine +haloperidol +diazepam	Day sleeping	PD
Chlorpromazine+haloperidol+lorazepam	Nettle rash	PD
		PK
Chlorpromazine +haloperidol+oxazepam	Day sleeping	PK
Chlorpromazine +risperidone	Acute dyskinesia	PD
Chlorpromazine+tropatepine+promethazine	Tachycardia	PD
Haloperidol+levomepromazine	Acute dyskinesia	PD
	Extrapyramidal symptoms	PD
Haloperidol+lorazepam	Insomnia	PD
		PK
Haloperidol+oxazepam+carbamazepine	Headache	PD
		PK
Risperidone + diazepam	Day sleeping	PD

PD : Pharmacodynamic; PK: Pharmacokinetic

Table 7: Side events related to drug-drug interactions.

this study is 8.86 mg/day. Several studies indicate that smaller doses up to 2 mg/day are as efficient with fewer side events [19-21].

Benzodiazepines are often combined to neuroleptics in psychiatry for better clinical results. The daily dose of diazepam, the most prescribed benzodiazepine in the present study is 13.33 mg while Glen et al. have suggested 54 mg for combinations [22]. The smaller dose of this study could be explained by the combination with antihistaminic. The high therapeutic observance by hospitalized patients compared to other studies [23,24] is due to the permanent presence of a care giver and to the psycho education given in the department. Two main types of side events have been recorded. The neurological ones (the most frequent) followed by appetite improvement. The frequency of neurological SEs is 61.58% against 79.10% in a study by Khoda et al. [13] in India. Day sleeping occurred in 17.44% of the cases during the first three days of treatment and can be related to the sedative property of neuroleptics (action on H1 histaminic, α1 adrenergic and M1 muscarinic receptors) and to benzodiazepines (potentializing the depressive effect of the GABAergic transmission). Benzodiazepines are able to increase the plasma levels of neuroleptics thereby maximizing their effects [25]. Gao et al. [26] study on Haloperidol in psychotic patients found the median time-to-day sleeping to be three days. Abnormal movements are caused by neuroleptics. Their prevalence in this study is 5.81%. A study by the American Psychiatric Association indicated 10% as the frequency of acute dyskinesia [27]. According to another study [28], 2 to 3% of patients put under neuroleptics develop a dyskinesia. The difference in these data is linkable to the profile of the molecules used. Weight gaining is a SE due to neuroleptics and can be explained by the improvement of the appetite. 4.65% of the patients experienced an increase of appetite; a number which is smaller than the

Side events	Number	Time-to-event (days)
Day sleeping	15	1;2;3
Better appetite	4	1;2;10
Headache	4	4;7;9;14
Accute dyskinesia	3	6;7;20
Vertigo	3	6;7 ;8
Asthenia	2	1;15
Orthostatic hypotension	2	1;7
Insomnia	2	10;24
Dry mouth	2	8;9
Anorexia	1	4
Muscule cramps	1	22
Dyspnoea	1	15
Arterial hypotension	1	1
Urinary incontinence	1	16
Muscule stiffness	1	2
Stereotypy of gestures	1	9
Extrapyramidal symptoms	1	20
Tachycardia	1	4
Ocular twitch	1	9
Neck stiffness	1	8
Trembling of the hands	1	3
Nettle rash	1	18
Swollen face	1	20
Vomiting	1	2

Table 8: Side events related to drug-drug interactions.

78% of Pérez-Iglesias et al.' in Spain [29]. This variation is explainable by difference of classes of the neuroleptics prescribed in both settings. The occurrence of SEs calls for measures that could improve patients' quality of life. Doses have been reduced in 23% of the cases against 36% in India [13]. Possible strategies of an active monitoring, which could enable physicians to a possible prevention, early detection and a timely management of such adverse events should be developed in the psychiatry setting.

Limitations

The size of our study population does not allow the observation of rare SEs that occurs in one patient out of a thousand. In addition, only clinical adverse events were collected since laboratory tests were seldom prescribed.

Conclusion

At the National University Hospital of Benin, the main psychiatric diseases are psychoses in hospitalized patients (61.11%) and depression in those followed ambulatory (38%). Typical antipsychotics are more prescribed (84.44%) than the second generation ones. Neuroleptics are more frequent in the treatment of hospitalized patients compared to external patients but the prescription of benzodiazepines does not vary in the two groups. Therapeutic observance is good (91.86%) but side events involve 65.12% of the patients. Drug doses are reduced only in 23% of the cases while the product is stopped in 5.77% of those situations. Other studies could be added to this one to analyze biological side events, assess the weight gain linked to neuroleptics and better describe drug-drug interactions in psychiatry. Atypical antipsychotics should be made more available and pharmacovigilance developed in the country by installing a National Pharmacovigilance Center and by training the health personnel.

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