
Non-Interventional Study (NIS) Synopsis

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**IBIS (Italian Burden of Illness analysis on Schizophrenia & bipolar disorder)
SYNOPSIS**

Objectives

Primary

- To describe the pharmaco-utilisation of antipsychotics (including typical and atypical) and the characteristics of patients affected by schizophrenia or BD.

Secondary

- To describe treatment adherence and costs in patients who switched from quetiapine immediate release (IR) to quetiapine extended release (XR).

Study design

IBIS was a multicentre, real-world, retrospective, observational cohort study of pharmac-utilisation data obtained from the administrative databases of Local Health Units (LHU) in Italy for patients with schizophrenia or BD (NCT01392482).

For the primary objective, patients were enrolled if they had filled at least one prescription for antipsychotics (ATC code N05A) between January 1st, 2008 and December 31st, 2009 (enrolment period). The enrolment date was defined as the first date on which a patient filled a prescription for an antipsychotic (the index date). Starting from the index date, patients were followed for 1 year and pharmaco-utilisation data collected. For the secondary objective, patients were enrolled if they had filled at least one prescription for quetiapine XR between January 1st, 2009 and June 30th, 2010 (enrolment period) and had been treated with quetiapine IR during the 6 months immediately preceding the enrolment date (enrolled patients could receive concomitant antipsychotics, but the largest number of refills must have been for quetiapine prescriptions). The analysis compared treatment adherence and costs during the 6 months preceding the enrolment (IR period) with those during the 6 months following inclusion (XR period).

Target subject population and sample size

Patients ≥ 18 years with a diagnosis of schizophrenia (ICD10: F20, ICD9: 295.XX) or BD (ICD10: F30-F31, ICD9: 296.XX excluding 296.2 and 296.3, depression) were enrolled.

The sample size was calculated based on the secondary analysis population involving patients switching from quetiapine IR to quetiapine XR. Assuming an effect size (mean of the difference divided by standard deviation of the difference) of 0.2, to achieve 80% power and alpha equal to 5%, at least 197 patients for the overall sample (both pathologies considered together) were necessary.

Investigational product and comparators: dosage, mode of administration and batch numbers

Not applicable

Duration of treatment

Not applicable

Variables

– Treatment adherence

Adherence was estimated by calculating the proportion of days covered (PDC) on which a patient had drugs available in the interval from their first purchase until the end of the follow-up period. The interval was separated into treatment episodes of continuous drug use based on Catalan's method [1]

– Cost of Illness & resources consumption

Services provided by Mental Health Departments, in particular residential access (nursing home, full day) and semi-residential access (nursing home, half day), outpatient specialist services; regional tariffs were used. The approach proposed by Weiden et al [2] was used to identify related hospitalisations; DRGs costs were used.

Other disease-related costs considered included antipsychotics and concomitant central nervous system drugs (ATC code N); the price at the moment of the purchase was used.

– **Comorbidities**

To characterize each patient according to his comorbidities, the Charlson Severity Index was used [3].

Statistical analysis

Continuous variables were reported as mean and standard deviation (median and range as appropriate), whereas categorical variables were expressed as numbers and percentages. When comparisons were made, groups were assessed and compared using t-tests and chi-square tests respectively (Mann-Whitney test or Wilcoxon if paired comparisons and Fisher exact test or McNemar if paired comparisons as appropriate). Two-tailed p-values less than 0.05 were considered significant. To understand which factors were associated to the therapeutic switch (from IR to XR quetiapine) and which factors were associated to a reduction in number of hospitalizations between the two periods in analysis, two multivariable logistic regression models were implemented; model calibration was assessed using Hosmer-Lemeshow test and model discrimination was assessed using c-statistic. All analyses were performed using STATA SE, version 12.0.

Primary analysis results

The primary design includes 12,943 beneficiaries (52% male, age 50.0 ± 14.6); patients affected by schizophrenia were 7,457 (58%), while patients with bipolar disorder were 5,486 (42%); patients on bipolar disorder were slightly older (52 years vs 48 of patients on schizophrenia) and more likely female (59% vs 40% of patients on schizophrenia) (Table P1).

Table P1. Demographic characteristics

	n	%	Age (mean±SD)
Female	6,223	48.1%	53.2 ± 14.7
Male	6,720	51.9%	47.1 ± 13.8
Schizophrenia	7,457	57.6%	48.4 ± 14.2
- Female	3,014	40.4%	52.6 ± 14.8
- Male	4,443	59.6%	45.6 ± 13.1
Bipolar Disorder	5,486	42.4%	52.2 ± 14.7
- Female	3,209	58.5%	53.7 ± 14.6
- Male	2,277	41.5%	50.1 ± 14.6
Total	12,943		50.0 ± 14.6

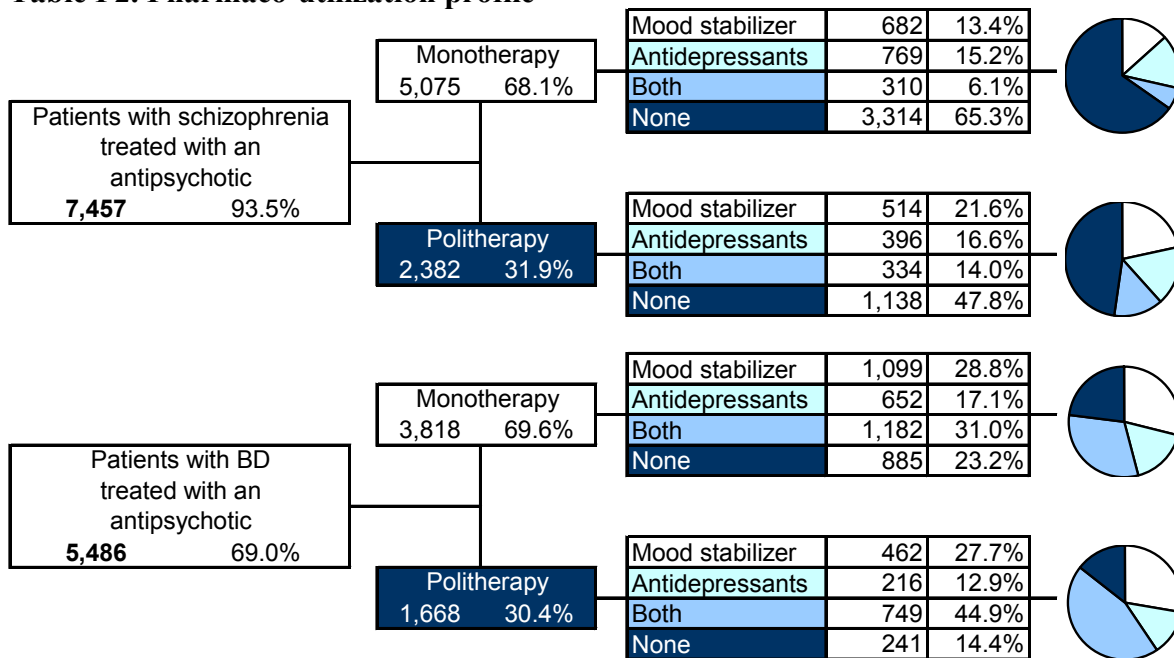
A high proportion of patients with bipolar disorder mania phase were observed (44%); this is probably because the mania phase is more severe and more often hospitalized than the depressive phase, and since the database used data retrieved from hospital or mental health department, those patients are more likely included; a high proportion of unspecified type was also observed (16%), depressive phase was 165, mixed 23%.

Pharmacoutilization

About two third of the sample (68% for schizophrenia, 70% for bipolar disorder) used monotherapy antipsychotics during the year of follow up.

A relevant proportion of patients affected by schizophrenia also received concomitant mood stabilizers and/or antidepressants (35% in monotherapy and 52% in politherapy group); compared with schizophrenia, a higher proportion of patients with BD received concomitant mood stabilizers and/or antidepressants (77% in monotherapy and 86% in politherapy group) (Table P2).

Table P2. Pharmaco-utilization profile



Across all patients with schizophrenia or bipolar disorder, 24 different antipsychotics were used.

The most commonly prescribed monotherapy for patients with schizophrenia was olanzapine (25%), followed by risperidone (18%) and haloperidol (16%); the most commonly prescribed monotherapy for patients with bipolar disorder was olanzapine (35%), followed by quetiapine (20%) and risperidone (12%) (Table P3).

Table P3. Pharmac-utilization in patients treated with a antipsychotic monotherapy

Antipsychotic	TOTAL		SCHIZOPHRENIA		BIPOLAR DISORDER	
	n	%	n	%	n	%
Olanzapine	2,613	29.4%	1,277	25.2%	1,336	35.0%
Risperidone	1,356	15.2%	915	18.0%	441	11.6%
Haloperidol	1,184	13.3%	815	16.1%	369	9.7%
Quetiapine	1,089	12.2%	325	6.4%	764	20.0%
Clozapine	895	10.1%	766	15.1%	129	3.4%
Aripiprazole	541	6.1%	278	5.5%	263	6.9%
Clotiapine	203	2.3%	118	2.3%	85	2.2%
Fluphenazine	184	2.1%	153	3.0%	31	0.8%
Levomepromazine	167	1.9%	87	1.7%	80	2.1%
Amisulpride	162	1.8%	68	1.3%	94	2.5%
Other	499	5.6%	273	5.4%	226	5.9%
Monotherapy	8,893	68.7%	5,075	68.1%	3,818	69.6%
Polytherapy	4,050	31.3%	2,382	31.9%	1,668	30.4%
	12,943		7,457		5,486	

For patients on politherapy, 644 combinations were observed overall; the more frequent 5 combinations are reported in Tables P4 and P5; those combinations were add-ons among 69% for patients with schizophrenia and 52% for patients with bipolar disorder, and switches among 31% for patients with schizophrenia and 48% for patients with bipolar disorder.

Table P4. Pharmac-utilization in antipsychotic politherapy patients - schizophrenia

SCHIZOPHRENIA		
Combination	n	%
Haloperidol Olanzapine	197	8.3%
Haloperidol Quetiapine	93	3.9%
Clozapine Haloperidol	90	3.8%
Haloperidol Risperidone	73	3.1%
Olanzapine Risperidone	63	2.6%
Other	1,866	78.3%
Total	2,382	
Add-on	1,643	69.0%
Switch	739	31.0%

Table P5. Pharmac-utilization in antipsychotic politherapy patients – bipolar disorder

BIPOLAR DISORDER		
Combination	n	%
Olanzapine Quetiapine	104	6.2%
Aripiprazole Olanzapine	89	5.3%
Haloperidol Olanzapine	80	4.8%
Haloperidol Quetiapine	76	4.6%
Aripiprazole Quetiapine	55	3.3%
Other	1,264	75.8%
Total	1,668	
Add-on	860	51.6%
Switch	808	48.4%

Cost Of Illness

The mean disease related costs per patient affected by schizophrenia totaled €4,157, with hospitalizations and nursing home covering 70% of the total costs and antipsychotics covering 24%; for bipolar disorder patients, total disease related costs were €3,301, with hospitalizations and nursing home covering 62% of the total costs and antipsychotics covering 27%; a higher cost for other Central Nervous System drugs was observed (€265 vs €98) (Table P6).

Table P6. Cost of illness

	Schizophrenia			Bipolar disorder		
	mean	SD	%	mean	SD	%
Antipsychotics (N05A)	1,018.81	1,213.58	24.5%	880.31	1,000.24	26.7%
Other drugs (CNS)	98.21	228.52	2.4%	264.87	364.18	8.0%
Ambulatory Services	128.85	372.64	3.1%	114.08	284.00	3.5%
Hospitalizations	1,128.01	3,779.11	27.1%	1,542.01	3,839.23	46.7%
Nursing home	1,783.56	6,173.32	42.9%	499.76	3,123.50	15.1%
TOTAL	4,157.44			3,301.03		

Secondary analysis results

Descriptives

The secondary design includes 319 beneficiaries (40% male, age 50.6 ± 14.6); patients affected by schizophrenia were 43%, while patients with bipolar disorder were 57% (Table S1).

As seen in the primary analysis, the most frequent bipolar disorder phase was mania (44%); a high proportion of patients received an unspecified bipolar disorder diagnosis (25%); depressive type represents 14% of the sample and mixed 16%..

Table S1. Demographic characteristics

Gender	Schizophrenia			Bipolar disorder		
	Age (mean±SD)	n	%	Age (mean±SD)	n	%
Female	53.1±14.1	77	56%	52.5±15.2	113	62%
Male	45.9±12.1	61	44%	48.6±15	68	38%
Total	49.9±13.7	138	43%	51±15.2	181	57%

Among schizophrenia patients, 73% had an IR dosage inside the range 300-800 mg and 75% had an XR dosage inside this range; percentage for bipolar disorder group were, respectively, 68% and 75%; mean ± Standard Deviation and median (InterQuartile Range) dosages are reported in Table S2.

Table S2. Dosages

		Schizophrenia	BD
QTP IR	Mean ± SD	494 ± 293	418 ± 250
QTP IR	Median (IQR)	428 (379)	395 (373)
QTP XR	Mean ± SD	508 ± 286	461 ± 261
QTP XR	Median (IQR)	426 (400)	400 (342)

Adherence

The adherence level between the two periods in analysis showed an increase for both pathologies ($p < 0.001$), more accentuated in the bipolar disorder group (+26.1% vs +12.4% of the schizophrenia group) (Table S4).

Table S4. Treatment adherence

Diagnosis	n	%	Adher.		p
			IRQ (mean±SD)	XRQ (mean±SD)	
Schizophrenia	138	43.3%	48.4 ± 23.9	60.8 ± 27.5	< 0.001
Bipolar Disorder	181	56.7%	42.5 ± 24.9	68.6 ± 25.4	< 0.001
Total	319		45.0 ± 24.6	65.2 ± 26.6	< 0.001

Cost Of Illness & resources consumption

Patients affected by schizophrenia showed a cost increase for antipsychotic drugs (+€539), which was completely offset by a cost reduction primarily related to ambulatory services (-€28) and, although not statistically significant, to a decrease in costs for hospitalizations (-€93) and nursing home (-€532) (Table S5); in relation to the latter, a reduction of average length of stay per patient was registered (from 15 to 11 days during the 6 month), while length of stay per single hospitalization was 15 days both in the IR and XR period (Table S6).

Table S5. Schizophrenia, Cost Of Illness

	IR period			XR period			Diff. €	Diff. %	p
	mean	SD	%	mean	SD	%			
Antipsychotics (N05A)	735.51	575.49	20.0%	1,274.27	815.78	36.0%	+538.76	+73.2%	0.000
Other drugs (CNS)	118.62	217.33	3.2%	95.98	210.03	2.7%	-22.64	-19.1%	0.026
Ambulatory Services	74.62	185.22	2.0%	46.87	134.08	1.3%	-27.75	-37.2%	0.004
Hospitalizations	1,013.17	376.40	27.5%	920.16	1,628.60	26.0%	-93.01	-9.2%	0.768
Nursing home	1,738.61	514.18	47.2%	1,206.18	630.33	34.0%	-532.43	-30.6%	0.184
TOTAL RELATED	3,680.53		91.3%	3,543.46		89.3%	-137.07	-3.7%	0.824
TOTAL UNRELATED	348.86		8.7%	424.95		10.7%	+76.09	+21.8%	0.593
GRAND TOTAL	4,029.39			3,968.41			-60.98	-1.5%	0.937

Table S6. Schizophrenia, Resources consumption

Pts.	IR period		XR period		p
	138		138		
RELATED					
Hospitalizations, pts (n, %, SD)	23	16.7%(3.2%)	27	19.6%(3.4%)	0.584
Hospitalizations, total	43		46		-
Hospitalizations (mean ± SD)	0.31	0.04	0.33	0.04	0.788
Length Of Stay (days, total)	653		674		-
Length Of Stay per hospital. (days, mean ± SD)	15.2	18.6	14.7	14.9	0.802
Length Of Stay per pts. (days, mean ± SD)	4.7	13.8	4.9	13.4	0.780
Nursing home, pts (n, %, SD)	24	17.4%(3.2%)	27	19.6%(3.4%)	0.505
Length Of Stay (days, mean ± SD)	15.0	43.6	10.8	30.5	0.170
Pts, ≥ 1 psychiatric visits, pts (n, %, SD)	81	58.7%(4.2%)	57	41.3%(4.2%)	0.000
Psychiatric visits (mean ± SD)	3.1	7.4	2.1	5.7	0.002
UNRELATED					
Other hospitalizations, pts (n, %, SD)	6	4.3%(1.7%)	6	4.3%(1.7%)	0.773
Pts, ≥ 1 other visits, pts (n, %, SD)	50	36.2%(4.1%)	41	29.7%(3.9%)	0.164

Patients affected by bipolar disorder showed a cost increase for antipsychotic drugs (+€584), which was completely offset by a statistically significant reduction in hospitalizations costs (-€1,088) (Table S7), due to a lower rate of hospitalized patients (23% vs 37%); length of stay

per single hospitalization was longer compared to hospitalizations for schizophrenia patients, and it was about 18 days both in the IR and XR period (Table S8).

Table S7. Bipolar Disorder, Cost Of Illness

	IR period			XR period			Diff. €	Diff. %	p
	mean	SD	%	mean	SD	%			
Antipsychotics (N05A)	584.74	487.76	16.9%	1,168.76	690.95	41.2%	+584.02	+99.9%	<u>0.000</u>
Other drugs (CNS)	178.59	273.22	5.2%	177.29	324.17	6.2%	-1.30	-0.7%	0.925
Ambulatory Services	98.11	228.42	2.8%	82.47	211.25	2.9%	-15.64	-15.9%	0.274
Hospitalizations	2,295.32	297.20	66.5%	1,206.84	189.61	42.5%	-1,088.48	-47.4%	<u>0.003</u>
Nursing home	297.20	5,717.88	8.6%	204.35	1,254.70	7.2%	-92.85	-31.2%	<u>0.456</u>
TOTAL RELATED	3,453.96		80.9%	2,839.71		85.4%	-614.25	-17.8%	0.263
TOTAL UNRELATED	816.90		19.1%	483.72		14.6%	-333.18	-40.8%	0.457
GRAND TOTAL	4,270.86			3,323.43			-947.43	-22.2%	0.274

Table S8. Bipolar Disorder, Resources consumption

Pts.	IR period		XR period		p
	181		181		
RELATED					
Hospitalizations, pts (n, %, SD)	67	37.0%(3.6%)	42	23.2%(3.1%)	<u>0.002</u>
Hospitalizations, total	103		67		-
Hospitalizations (mean ± SD)	0.57	0.04	0.37	0.04	<u>0.017</u>
Length Of Stay (days, total)	1,785		1,302		-
Length Of Stay per hospital. (days, mean ± SD)	17.3	34.9	19.4	38.9	0.525
Length Of Stay per pts. (days, mean ± SD)	9.9	18.3	7.2	14.6	<u>0.023</u>
Nursing home, pts (n, %, SD)	15	8.3%(2.0%)	13	7.2%(1.9%)	0.789
Length Of Stay (days, mean ± SD)	2.7	15.5	1.8	8.2	0.402
Pts, ≥ 1 psychiatric visits, pts (n, %, SD)	112	61.9%(3.6%)	87	48.1%(3.7%)	<u>0.000</u>
Psychiatric visits (mean ± SD)	3.7	6.0	2.6	5.1	<u>0.005</u>
UNRELATED					
Other hospitalizations, pts (n, %, SD)	11	6.1%(1.8%)	12	6.6%(1.8%)	0.070
Pts, ≥ 1 other visits, pts (n, %, SD)	92	50.8%(3.7%)	74	40.9%(3.7%)	<u>0.016</u>

Summary of pharmacokinetics: not applicable

Summary of pharmacogenetics: not applicable

Summary of safety results: not applicable

References

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