Original Articles

Understanding antipsychotic non-classical prescriptions: a quantitative and qualitative approach

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SUMMARY. **Aims** – To date only a few studies investigated the clinical reasons supporting and explaining non-classical antipsychotic prescriptions. The present study was carried out to develop concepts which help understand this phenomenon in a natural setting, giving emphasis to views of clinicians according to quali – quantitative research methodologies. **Subjects** – From the South-Verona Psychiatric Case Register all antipsychotic prescriptions issued during 2005 were extracted. Concurrent prescribing of two or more antipsychotics, prescribing antipsychotic drugs outside the licensed indications, and outside the licensed ranges of doses reported in the Italian National Formulary, were considered non-classical prescriptions. Reasons for non-classical prescriptions were collected by means of brainstorming sessions with clinicians. Non-classical prescriptions and the corresponding reasons were grouped according to whether they were "clinically sound" or "clinically not sound". **Results** – During 2005 a total of 259 patients received 376 non-classical prescriptions. The most frequently reported reasons for non-classical prescribing were that prescriptions were inherited from another clinician with or without benefit, and that prescriptions were motivated by the need of reducing psychotic symptoms. More than 60% of these non-classical prescriptions were categorised as "clinically sound". Clinically not sound prescriptions were related with negative clinicians' views and opinions about the patient/clinician relationship. **Conclusion** – Clinically not sound prescriptions appeared just a reflection of a problematic doctor/patient relationship, where no individual treatment plan existed and psychiatric visits had the only goal of monitoring ongoing prescriptions.

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KEY WORDS: antipsychotics; epidemiology; community psychiatric services; irrational prescriptions.

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INTRODUCTION

Many epidemiological surveys carried out in different settings and countries consistently documented that a relevant proportion of psychiatric patients are exposed to non-classical antipsychotic (AP) prescriptions, that is prescriptions that do not follow accepted principles of prescribing (Kingsbury *et al.*, 2001). Three categories of non-classical prescriptions have often been documented: (a) polypharmacy, that is the concurrent prescribing of two or more AP drugs (Ganguly *et al.*, 2004; Biancosino *et al.*, 2005; Centorrino *et al.*, 2005; Ananth, 2005); (b) off-label prescribing, that is prescribing AP drugs outside the licensed indications (Weiss *et al.*, 2000; Barbui *et al.*, 2004; Percudani *et al.*, 2006); (c) off-label dosages, that is prescribing AP drugs outside the licensed ranges of doses (Rijcken *et al.*, 2003; Kogut *et al.*, 2005; Barbui *et al.*, 2006).

Very surprisingly, however, only a few studies investigated the clinical rationales supporting and explaining non-classical AP prescribing. Sernyak and Rosenheck, who reviewed the treatment of 66 patients with schizophrenia, showed that frequently reported clinicians' reasons for AP polypharmacy included the attempt of reducing positive symptoms, negative symptoms and extrapyramidal side effects (Sernyak & Rosenheck, 2004). Similar findings were found by Tapp and colleagues and Schumacher and colleagues (Tapp *et al.*, 2003; Schumacher *et al.*, 2003), who emphasised the

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views expressed by clinicians that some non-classical prescriptions were "clinically sound".

In the present study we investigated the phenomenon of non-classical AP prescribing in an epidemiologically representative sample of psychiatric patients living in the community. The aim was to develop concepts which help understand this phenomenon in a natural setting, giving emphasis to views of clinicians according to qualitative research methodologies. Qualitative approaches are nowadays essential components of health services research, and techniques such observation, interviews and focus groups are considered preliminary steps to quantitative research; they can be used as supplements to quantitative work as part of a multimethod approach; finally, they enable to access areas not amenable to quantitative research. The goal of qualitative research is the development of concepts which help understand social phenomena in natural (rather than experimental) settings (Pope & Mays, 1995).

METHODS

Setting

This study was conducted in South-Verona, Italy (about 100,000 inhabitants), an area that includes part of the city of Verona and three neighbouring small towns. The main agency providing psychiatric care for the adult population is the South-Verona community mental health service (CMHS). The CMHS is a unitary service, in which great emphasis is given to communication between all staff members and to integration between the various clinical activities. The CMHS comprises one inpatient unit located in the general hospital and a network of outpatient and community facilities (Tansella *et al.*, 2006a; Tansella & Burti, 2003).

Data source

In the catchment area of South-Verona, since 1978, the year of implementation of the Italian psychiatric reform, the South-Verona Psychiatric Case Register (PCR) routinely records, for all subjects in contact with the CMHS, socio-demographic characteristics, ICD-10 diagnoses, past psychiatric and medical history, clinical data (including Global Assessment of Functioning [GAF] scores), admissions and outpatient contacts (Amaddeo *et al.*, 1997). The PCR also records details of patients who leave the catchment area, and those who die. The PCR, however, does not routinely collect information on prescriptions of psychotropic drug. In an effort to fill this lack of data, in 2003 a psychotropic drug registry (PDR) was developed and implemented (Barbui *et al.*, 2005). The registry can be accessed using most Internet browsers from any personal computer located within the psychiatric service. The system works in such a way that physicians, when prescribing a medication for the first time, store that prescription in the registry. During the following outpatient contacts, physicians don't need to add any further information, or modify the existing information, if prescriptions are adhered to and if the therapeutic regimen remains unchanged. However, if a prescription is stopped (or increased/decreased, or if the prescribed drug was not taken) the registry needs to be updated, as well as if a new prescription is issued to that specific patient. Information stored in the PDR is regularly cross-checked with information stored in patients' clinical records. In case of inconsistencies, the treating physician is contacted for updating the system (Barbui *et al.*, 2005; Bonetto *et al.*, 2006).

Data extraction

From the South-Verona PCR all patients with at least one psychiatric contact with the CMHS during the year 2005 were identified. For each included subject, sociodemographic and clinical data were extracted. Using the PCR patient code (a code that uniquely identifies individuals), individuals who were exposed to APs (pharmacological agents from the N05A group, excluded lithium, of the anatomical therapeutic chemical [ATC] classification system) during 2005 were extracted from the PDR. For each individual exposed to APs, the drugs' names, dates of prescription and prescribed daily doses were extracted.

Prescriptions meeting at least one of the following three conditions were considered non-classical AP prescriptions: (a) concurrent prescribing of two or more APs (polypharmacy) (National Institute for Clinical Excellence, 2002); (b) off-label prescribing, that is prescribing AP drugs outside the licensed indications reported in the Italian National Formulary; (c) off-label dosage prescribing, that is prescribing AP drugs outside the licensed ranges of doses reported in the Italian National Formulary.

Clinicians' reasons for antipsychotic non-classical prescriptions

To study reasons for AP non-classical prescriptions, a qualitative methodology was employed (Pope & Mays,

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1995). A brainstorming session was held for each clinician who issued irrational prescriptions. During the session, clinicians were invited to generate statements focusing on factor(s) that were responsible for each prescription. Additionally, for each patient to whom the prescription referred, clinicians were invited to describe the main characteristics of the psychiatric visits and the main aspects related to the doctor/patient relationship.

In a subsequent stage, two researchers (MN and CB) not involved in the brainstorming sessions independently reviewed all generated statements and reasons for AP non-classical prescriptions. Repetitive or overlapping statements were combined into single statements, and a final list of reasons was generated.

Finally, the two researchers not involved in the brainstorming sessions grouped non-classical prescriptions and the corresponding reasons according to whether they were "clinically sound" or "clinically not sound". Non-classical prescriptions were considered clinically sound when reasons included one of the following statements: "inherited from another prescriber with benefit"; "reduced psychotic symptoms"; "increased sedation"; "reduced adverse effects"; "switching/stopping"; "diagnosis still unclear". Non-classical prescriptions were considered clinically not sound when reasons included one of the following statements: "inherited from another prescriber with no benefit"; "no reason"; "polypharmacy to increase adherence"; "off-label prescribing to increase adherence"; "polypharmacy to increase sedation".

Data analysis

Categorical data were analysed by chi-square statistics, and Mann-Whitney two-sample statistics were used to analyse continuous data which were not normally distributed.

RESULTS

Prevalence of non-classical prescribing

During 2005 a total of 516 patients were exposed to AP drugs. Of these, 259 (50%) patients received 376 non-classical prescriptions. Polypharmacy accounted for 26.9% of non-classical prescriptions, off-label prescribing for 47.9% and off-dosage prescribing for 25.2% of non-classical prescriptions.

Clinicians' reasons for antipsychotic non-classical prescriptions

Clinicians' reasons for AP irrational prescriptions are presented in Table I. The most frequently reported statements were that prescriptions were inherited from another clinician with or without benefit, and that prescriptions were motivated by the need of reducing psychotic symptoms. The categorization of non-classical prescriptions into clinically sound and clinically not sound prescriptions, based on the reasons provided by clinicians, revealed that more than 60% of non-classical prescriptions were clinically sound (Table II). AP prescriptions were issued by 25 psychiatrists, 21 of whom issued both clinically sound and clinically not sound prescriptions.

Table II – *Categorization of non-classical prescriptions into clinically sound and clinically not sound prescriptions.*

	Clinically sound prescriptions			
	Yes N=233		**No N=143**	
	N	**%**	**N**	**%**
Polypharmacy	59	25.3	42	29.4
Off-label	106	45.5	74	51.7
Over/Under Treatment	68	29.2	27	18.9
Total	233	100.0	143	100.0

Table I – *Clinicians' reasons for antipsychotic non-classical prescriptions.*

	Polypharmacy		**Off-Label**		**Outside dose range**	
	101 prescriptions		180 prescriptions		95 prescriptions	
Reason	N	%	N	%	N	%
Inherited from another prescriber with benefit	19	18.8	27	15.0	21	22.1
Inherited from another prescriber with no benefit	24	23.8	42	23.3	17	17.9
Reduced psychotic symptoms	14	13.9	46	25.6	27	28.4
Increased sedation	10	9.9	26	14.4	12	12.6
Reduced adverse effects	4	3.9	3	1.7	2	2.1
Switching/stopping	22	21.8	0	0	6	6.4
Increased adherence	4	3.9	4	2.2	0	0
No reason	4	3.9	28	15.6	10	10.5
Diagnosis still unclear	0	0	4	2.2	0	0

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Factors associated with clinically sound and clinically unsound prescriptions

The analysis of factors associated with clinically sound and clinically unsound prescriptions revealed that patient characteristics were similarly distributed between the two groups (Table III). By contrast, characteristics related to the doctor/patient relationship were not similarly distributed between the two groups (Table IV). Clinically sound prescriptions were more frequent when the main intervention was psychotherapy or psychological support, when psychiatric visits were judged useful by the treating clinicians, and when the doctor/patient relationship received a positive judgment by the treating clinicians (Table IV).

Table III – *Sociodemographic and clinical characteristics of patients receiving clinically sound and clinically not sound prescriptions.*

Patient characteristic	**Patients receiving clinically sound prescriptions only**				**Chi Square**	**Mann-Whitney Test**	
	Yes N=156		**No N=103**				
	N	%	N	%		**z**	**p**
Sex							
Males	75	48.1	51	49.5	p = 0.821		
Females	81	51.9	52	50.5			
Marital status							
Married	93	59.6	54	52.4	p = 0.253		
Single	63	40.3	49	47.5			
School level							
≤ 8 years	65	41.6	48	46.6	p = 0.433		
> 8 years	91	58.3	55	53.4			
Employment							
Not employed	111	71.1	75	72.8	p = 0.771		
Employed	45	28.8	28	27.1			
ICD-10 Diagnoses							
Psychotic disorders	47	30.1	31	30.1	p = 0.05		
Affective disorders	47	30.1	22	21.3			
Anxiety disorders	7	4.4	13	12.6			
Personality disorders	25	16.0	11	10.6			
Other disorder	30	19.2	26	25.24			
Mean age (SD)	50.8 (16.1)		51.3 (17.3)			-0.217	0.828
Mean GAF score (SD)	53.6 (13.0)		54.1 (13.2)			-0.075	0.940
Mean lenght of illness, years (SD)	11.0 (8.9)		10.9 (9.3)			0.506	0.613

Table IV – *Distribution of clinically sound and clinically not sound prescriptions by patient/clinician relationship.*

Patient characteristic	**Clinically sound prescriptions**				**Chi Square**
	Yes N=233		**No N=143**		
	N	%	N	%	
Main focus of the visits					
Psychotherapy	24	10.7	8	7.8	p = 0.003
Psychologiccal support	118	52.7	36	35.3	
Drug administration only	82	36.6	58	56.9	
Therapeutic utility of the psychiatric visits according to the clinician's subjective opinion					
Useful	139	62.6	53	51.0	p = 0.046
Useless	83	37.4	51	49.0	
Therapeutic value of the doctor/patient relationship according to the clinician's subjective opinion					
Negative	53	27.6	38	45.2	p = 0.004
Positive	139	72.4	46	54.8	

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DISCUSSION

The present study documented that non-classical AP prescriptions were issued to fifty percent of patients exposed to AP drugs.

However, there are some important limitations. The main limitation of this analysis is that it was conducted on a single psychiatric facility, and views and opinions might not reflect those of clinicians working in other settings of psychiatric care. Although we acknowledge this limitation, it should be considered that qualitative methods usually do not aim for reliability (that is, consistency on retesting) through the use of tools such as standardised questionnaires or through the use of randomly selected samples of health facilities (Mays & Pope, 2000; Stiles, 1999). Qualitative methods usually aim for validity, by getting at how people really behave and what people actually mean when they describe their behaviour. These methods, by reaching the parts other methods cannot reach, are nowadays considered an essential component in health and health services research.

Despite the limitations, the analysis of clinicians' reasons highlighted two interesting aspects. First, clinicians' reasons were very similar to those reported in studies carried out in the US, where the need of reducing psychotic symptoms, or adverse side effects, was a very commonly reported justification for AP polypharmacy (Sernyak & Rosenheck, 2004; Tapp *et al.*, 2003; Schumacher *et al.*, 2003). Second, clinicians' explanations for non-classical prescribing were rated as clinically sound in 60% of cases. In other words, in 60% of cases clinicians explained that after treatment guidelines were followed with no patient benefit, pharmacological strategies not supported by any evidence were attempted, with occasional improvements in terms of psychopathology or side effect profile. These views noticeably centre the problem of the existing discrepancy between typical clinical reasoning under real-world circumstances, where therapeutic answers need to be provided even in absence of randomised evidence, and the experimental world of treatment guidelines, where, necessarily, only therapeutic interventions backed by randomised evidence are recommended (Barbui, 2005). According to clinicians' views, a substantial proportion of non-classical prescriptions was motivated by the lack of evidence-based alternatives. Obviously, much still has to be done to reduce the discrepancy between research and practice, but recent renewed emphasis given to the need of developing pragmatic or practical trials, oriented to answer clinically meaningful research questions with designs resembling as much as possible ordinary circumstances, seems a very relevant step in this direction (March *et al.*, 2005; Tansella *et al.*, 2006b; Treweek *et al.*, 2006; Barbui *et al.*, 2007).

Another interesting insight derived from the present study is the analysis of factors associated with clinically sound and clinically unsound prescriptions. This analysis was quali-quantitative and had not the goal of testing any hypothesis, rather the reasoning was held to be inductive and hypothesis generating. We observed that clinically not sound prescriptions were not related with patient characteristics, but with clinicians' views and opinions about the therapeutic role of the patient/clinician relationship. In this sense the main finding of this analysis is that clinically not sound prescriptions appeared just a reflection of a problematic doctor/patient relationship, where no individual treatment plan existed and psychiatric visits had the only goal of monitoring ongoing prescriptions. The finding that psychiatric visits with a specific focus on psychotherapy or on psychological support were less likely to be associated with clinically not sound prescriptions was paradigmatic in this perspective.

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