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[Faculty of Science
Pharmaceutical Sciences]

The association between patient reported drug taking and gaps and overlaps in antidepressant drug dispensing

Helga Gardarsdóttir, PharmD
Toine CG Egberts, PhD
Eibert R Heerdink, PhD

ESPACOMP Bangor, 2009

Conflict of interest

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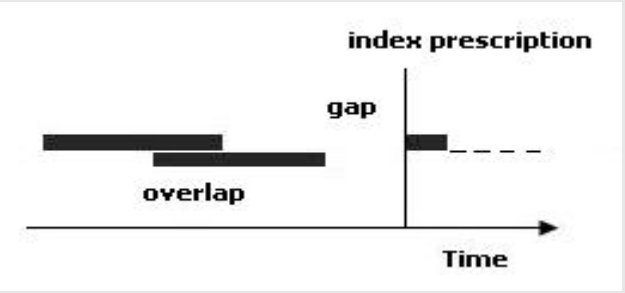
This research was financed by Utrecht University and received no addition funds.

Background

- Antidepressants
  - 2-4 weeks to become effective
  - 22% only receive a single prescription
  - Up to 66% discontinue within six months
- Patients use antidepressants differently from clinician recommendations

Background

- Adherence and persistence measurements
  - Prescribing or dispensing data
- Patients prescription "pick-up" patterns often seems irregular
  - Drug treatment patterns in databases show overlaps and gaps
- The real reason for the observed gaps and overlaps in prescribing/ dispensing databases is unknown



Aim

- To investigate if patient reported drug taking is associated with gaps and overlaps in antidepressant drug dispensing

Setting

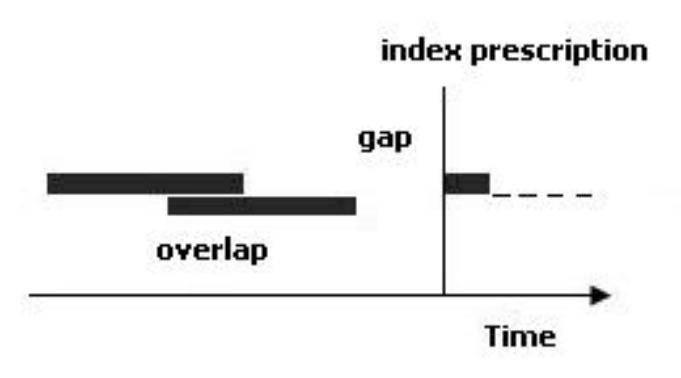
- Utrecht University Pharmacy Practice Research Network (UPPER)
  - >850 community pharmacies in the NL
  - Automated dispensing records
  - Virtually all Dutch inhabitants registered with a single pharmacy
- 37 of 46 approached pharmacies participated
- Pharmacies located in urban en rural areas

Study population

- Patients 18 years or older
- Random sample of 12-15 patients per pharmacy
  - Collected an SSRI or Venlafaxine (index date) during September throughout December 2008
- Received at least three antidepressant prescriptions belonging to the same treatment episode
- Prescription was considered to belong to the same treatment episode when less than 90 days elapsed from the last dispensed dose of a prior prescription and the collection of a subsequent prescription

Study Design

- Patient reported drug taking
  - Questionnaire
    - Medication Adherence Rating Scale (MARS)
    - Sociodemographic characteristics
    - Medication and disease characteristics
- Gaps and overlaps in treatment pattern
  - Two latest dispensing moments prior to index date
  - Length of overlap or gap measured
  - Gap or overlap presented as % of total observed treatment time



Data analysis

- Descriptive statistics
- Three groups and three sub-groups
  - Overlap
    - <5 %, ≥5% but <20%, ≥20% of observed treatment time (OTT)
  - Gap
    - <5 %, ≥5% but <20%, ≥20% of observed treatment time (OTT)
  - No overlap/gap
- Sub-group comparisons using Fisher's exact test
- Continuous variables comparison using Mann Whitney test
- Chronbach's alpha estimation of MARS internal consistency

Results

Table 1. Baseline characteristics of the study population on index date.

	n=205 (100.0 %)
Sociodemographic characteristics	
Female gender	129 (62.9)
Age	
18-30 years	25 (12.2)
31-45 years	61 (29.8)
45-60 years	87 (42.4)
>60 years	32 (15.6)
Education	
Low	57 (27.8)
Middle	83 (40.5)
High	60 (29.3)
Having a partner	118 (57.6)
Employment or in school	105 (51.2)
Living with others	141 (68.8)
Medication and disease characteristics	
Type of antidepressant	
Paroxetine	88 (42.9)
Citalopram	48 (23.4)
Fluoxetine	24 (11.7)
Other	45 (22.0)
Reason for use	
Depression	154 (75.1)
Anxiety	100 (48.8)
Total observed treatment time, median (IQR) days	119.0 (108.5)
Duration of each prescription prior to index date, median (IQR) days	47.5 (60.0)

Results

Table 2. Patient reported drug taking per group (gap, overlap, no gap or overlap) and subgroup (% of observed treatment time, OTT).

	Adherent (MARS) n (%)	MARS Median (IQR)	Stopped n (%)	Use differently n (%)
All patients (n=205)	153 (74.6)	24.0 (2.0)	6 (2.9)	38 (18.5)
Gap days				
Any (n=147)	107 (72.8)	24.0 (2.0)	5 (3.4)	31 (21.0)
<5% of OTT (n=40)	38 (95.0)[a]	25.0 (1.0)[b]	0 (0.0)	6 (15.0)
≥5% and <20.0% of OTT (n=45)	36 (80.0)[a]	24.0 (2.0)[b]	1 (2.2)	6 (13.3)
≥20% of OTT (n=62)	33 (53.2)	23.0 (4.0)	4 (6.5)	19 (30.7)
Overlapping days				
Any (n=53)	41 (77.4)	24.0 (1.5)	1 (1.9)	7 (13.2)
<5% of OTT (n=20)	18 (90.0)	25.0 (1.0)[b]	1 (5.0)	2 (10.0)
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a Fischer's exact test, $p<0.01$. Reference group = gap ≥20% of OTT
b Mann Whitney test, $p<0.05$. Reference group = gap/overlap ≥20% of OTT
MARS adherent = all questions answered with "never" or "rarely"

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Discussion and conclusions

- Patients with large gaps engage more frequently in non-adherent behavior than those with small gaps
- However, not all patients with large gaps report to engage in non-adherent behavior
- How well do definitions used to classify adherent drug taking actually include adherent patients
- Various reasons for seeing gaps for adherent patients

Thank you

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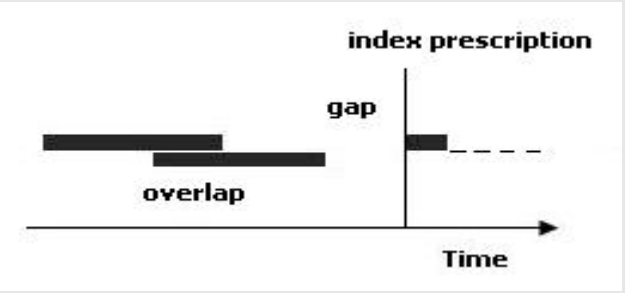

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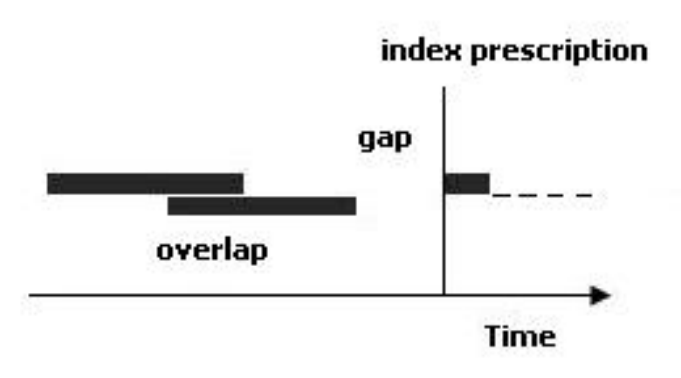

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NONCOMPLIANCE TO SIROLIMUS IN RENAL TRANSPLANTATION

Clara Sequeira[1], Odete Isabel[1], Alfredo Mota[2] and Carlos Fontes Ribeiro[3]

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- Medication noncompliance is a recognized, non-modern, multidimensional problem (Fig. 1), prevalent in all medical specialities, that accounts for treatment failure.
- Noncompliance estimates are variable in scientific literature due, primary, to methodological difficulties of the evaluation.
- In renal transplantation, noncompliance to immunosuppressives is insufficiently studied and defined, although can cause serious/devastating clinical (e.g., graft rejection or loss and, ultimately, death) and economic consequences.

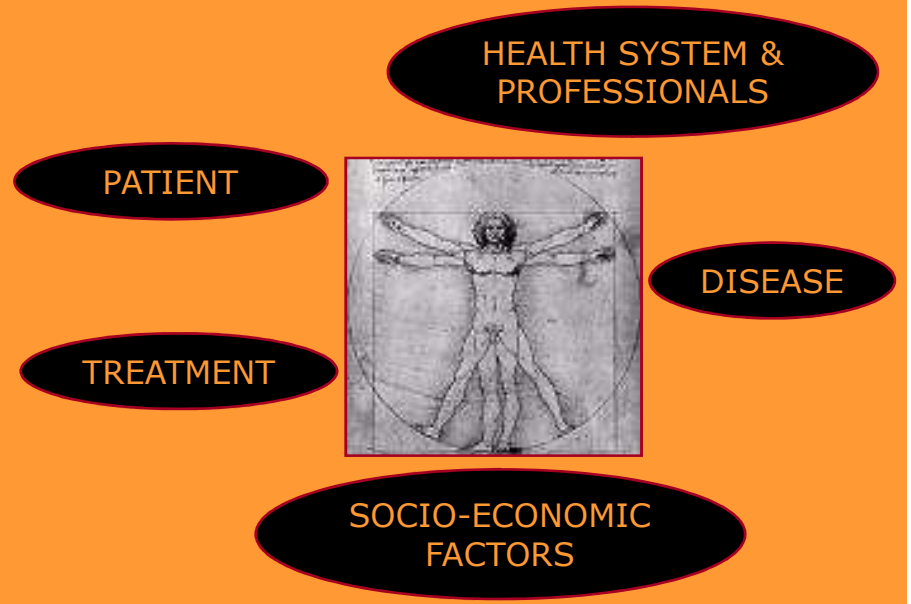

Fig. 1 – The five compliance dimensions

Compliance evaluation difficulties

1st difficulty related to ***COMPLIANCE METHODS***

DE GEEST et al., 1999; FARMER, 1999; MYERS et al., 1998; WHO, 2003

- There is no "gold standard";
- Several investigators study different factors, using various techniques and experimental designs, for different periods of time.

2nd difficulty related to ***COMPLIANCE OPERATIONAL DEFINITIONS***

DE GEEST et al., 1999

- They are investigator, study and method dependent;
- Compliance phenomenon is continuous and multidimensional;
- Patient categorization should be in accordance to a clinical meaningful definition:
  - *Frequency of adherence associated to the desired clinical effect, and/or*
  - *Frequency of non-adherence related to the increased risk of negative outcomes.*
- The 80% compliance rate "cut-off" level, frequently used in literature, is controversial and arbitrary …

Ideally, in renal transplantation, non-adherence should be defined as:

"amount of non-administered medication related to the increase risk of significant negative clinical events, such as rejection episodes and/or graft dysfunction or graft loss"

... **HOWEVER**, that is an **unknown value** !!!

and investigators opinions are not consensual ! BUTLER et al., 2004

In various studies on this matter, estimates have been variable:

- Frequency of non-adherence to immunosuppressants **2-68%** (BIHL, 2003; CHISHOLM, 2002), with a **25%** mean value (RUSSEL et al., 2004);
- BUTLER et al. (2004) meta-analysis (325 studies, renal transplant patients, published from 1980 to 2001, N=36):
  - Cross-sectional (N=15) (questionnaires) - **22% non-adherence** (median)
  - Cohort studies (N=10) - **36% graft loss** (median) associated to noncompliance
  - Non-adherence to immunosuppressants is common and has a great impact on graft survival

AIM OF THE STUDY

1) Measure, using four methods, the extent of noncompliance to Sirolimus (SRL) in renal transplantation;

   Sirolimus - mTOR inhibitor; oid; frequent dose in stable patients: 2-5 mg/day; trough levels in total blood (C_0) correlate well with drug exposure; frequent adverse events: leucopenia/thrombocytopenia, anaemia, hypercholesterolemia/hypertriglyceridemia, interstitial pneumonite, lymphocele, oedemas and difficult hound healing (DANOVITCH, 2001; GASTON, 2001; VASQUEZ, 2000)

2) Compare the compliance results of other methods to those of Electronic Monitoring (EM) (the closest to the “gold standard”);

3) Generate hypotheses on potential noncompliance risk factors (EM-based).

METHODS/MATERIALS

a) Ethics Committee Approval and Hospital Administration Authorization;

b) Setting: Outpatient Renal Transplantation Unit and Pharmacy Department;

c) Patient Information Document delivery (with EM compliance instructions) & Informed Consent obtained;

d) Exclusion criteria: illiteracy/personal limitation obstructing self-administered questionnaires;

e) Studied subjects: **N=31** patients administering SRL, attending clinical visits;

f) Design: observational/prospective (140±32 days` duration study; 9±4 visits);

g) Compliance methods:

Pills counting (PC) - during study period, using study drug prescription/dispensing/devolution records. Free study drug provided by the ambulatory care pharmacy.

Monitoring of blood levels (MBL) - performed at the end of study, collecting C_0/visit retrospectively. SRL half-life in renal transplant patients = 57-63h. Methods: HPLC/UV at beginning, after MEIA (Abbott-IMx®); authors used the 20% ⊕ bias of immunoassay in relation to chromatography to convert values, assuring comparability (IMx-based).

Electronic monitoring (EM) - during study period. Material acquired to AARDEX® Ltd. (MEMS® 6 TrackCap 38mm), with Wyeth and Fujisawa financial support. Compliance Report (Fig. 2) emitted at the end of the study.

Compliance self-reporting (CSR) - performed at final visit, using “Brief Medication Questionnaire, or BMQ, (2003) - Adapted” from SVARSTAD et al. (1999), with authors permission; “feed-back” of “last week” to assess compliance.

NONCOMPLIANCE TO SIROLIMUS IN RENAL TRANSPLANTATION

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METHODS/MATERIALS

Fig. 2 - Compliance Report (e.g.)

h) Compliance operational definitions according to methods and investigators criteria (Table 1). Compliance rate (CR) expressed by median ($Percentile_{25}$-$Percentile_{75}$) except for MBL (normal distribution); generally, Adherents/Non-adherents categorization based on a 80.0% CR “cut-off” level;

NONCOMPLIANCE TO SIROLIMUS IN RENAL TRANSPLANTATION

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METHODS/MATERIALS

Table 1 – Compliance operational definitions

METHODS	COMPLIANCE VARIABLES	
PC	CR (%)	$\frac{\text{Total taken/used dose (mg)}}{\text{Total prescribed/expected dose (mg)}} \times 100$
	ADHERENTS/NON-ADHERENTS CLASSIFICATION	Adherent – CR ≥ 80.0%; Non-adherent – CR < 80.0%
MBL*	CR (%)	$\frac{\text{Number of } C_0 \text{ reaching target levels ([8-12ng/ml])}}{\text{Number of } C_0 \text{ obtained/recorded}} \times 100$
	ADHERENTS/NON-ADHERENTS CLASSIFICATION (using CR)	Adherent – CR ≥ 80.0%; Non-adherent – CR < 80.0%
	ADHERENTS/NON-ADHERENTS CLASSIFICATION (using MEAN LEVELS)	Adherent – Mean C_0 reaching target levels; Non-adherent – Mean C_0 not reaching target levels
EM	CR "according to dose" (%)	$\frac{\text{Number of taken/presumed doses}}{\text{Number of prescribed doses}} \times 100$
	CR "according to doses interval" (%) [Correct/allowed (±25%) interval (24h/18-30h)]	$\frac{\text{Number of doses taken on schedule}}{\text{Number of prescribed doses}} \times 100$
	"Drug holidays"	One day (correct theoretical doses interval + 24h): 48-72h; Each 24h period increases "Drug holidays" 1 more day
	CR "according to days" (%)	$\frac{\text{Number of days with correct number of doses taken}}{\text{Number of monitored days}} \times 100$
	ADHERENTS/NON-ADHERENTS CLASSIFICATION	Adherent – 3 described CRs ≥ 80.0%; Non-adherent – At least one of the 3 described CRs < 80.0%
CSR	ADHERENTS/NON-ADHERENTS CLASSIFICATION	Adherent – Absence of noncompliance self-reporting; Non-adherent – Presence of noncompliance self-reporting

*Outpatient renal transplantation unit target levels in clinical practice 8-12ng/ml

i) Noncompliance risk factors id: patient interview, medical records/prescriptions, transplants database, Compliance Report & Quality of Life (QoL) questionnaire

(Self-perceived QoL assessed, at final visit, by self-administered "End-Stage Renal Disease Symptom Checklist – Transplantation Module, or ESRD-SCL" by FRANKE et al. (1999), with authors permission).

***Statistical analysis* (SPSS 11.5):** (1) Compliance data: a) testing differences - Wilcoxon`s matched-pairs & McNemar`s tests; b) testing associations - Spearman's & Fisher's exact tests; (2) Noncompliance risk factors - testing differences between Adherents/Non-adherents: Student's t or Mann-Whitney U tests & $\chi 2$ or Fisher's exact test . Statistical significance threshold $p<0.05$ (N.S. – Not statistically significant).

RESULTS

Baseline group's characteristics (N=31)

- 61.3% male patients
- Age = 47±11 (18-63) years old
- Mean BMI = 25.5 Kg/m^2
- 96.8% caucasian
- 71.0% married
    - Most patients had low scholar qualifications (58.1%) and were retired (61.3%)
    - 45.2% of the domestic aggregates had 3 elements
    - Monthly net income "*per capita*" was low (335±196 €)
- Pre-transplant dialysis duration = 41±31 months
- More frequent renal failure etiology was the indeterminate (32.3%)
- 93.5% patients received cadaveric donor grafts
- Mean time since transplantation was ≈ 24 months (re-transplanted patients = 0)
- Concomitant diseases were highly prevalent (80.6%)
- 7 patients had alcohol consumption habits (most frequent daily dose = 12 g)
    - Baseline nº of drugs was elevated: 8±2
    - Immunosuppression was primarily triple (87.1%), mostly of the SRL+ Mycophenolate mofetil+Prednisone type (SRL daily dose = 4±2 mg)

RESULTS

In MBL, nº of C_0 was 8±4 (1-15) (⇔ 90.3%). 41.2% of mean C_0/visit reached target levels (N=2 with C_0 abnormally high). C_0 (%) above and under target levels was similar. Mean C_0/patient was 11.6±3.4 (5.6-21.0) ng/ml.

In EM, nº of monitored days was 131±28 (55–215). Median time of the majority of taken doses was 8-9h (38%). 51.6% of patients had "Drug holidays" (most frequently of 1-day duration). Doses interval (median): shortest = 9h; longest = 48h.

Compliance rates are shown in Table 2. Except for MBL, CRs were high (≥ 90%).

Table 2 – Compliance rates according to the methods used

Methods / Measure	PC	MBL	"according to dose"	EM "according to doses interval"	"according to days"	CSR
CR (%)	**99.7** **(97.7 – 100.5)** 97.9 ± 6.4 (75.8 – 105.8)	50.0 (25.0 – 71.4) **50.3 ± 26.7** **(0.0 – 100.0)**	**99.3** **(97.7 – 100.7)** 97.2 ± 11.3 (47.9 – 115.7)	**89.7** **(83.9 – 97.6)** 87.8 ± 15.4 (32.6 – 100.0)	**95.0** **(88.6 – 99.2)** 91.2 ± 11.7 (46.5 – 100.0)	–

CR expressed, in the first line, by median ($Percentile_{25}$-$Percentile_{75}$) and, in the second, by mean±standard deviation (Minimum-Maximum)

When testing ***differences*** in CRs in relation to EM, we found that:

CR of PC was **superior** to the CRs of EM, except for CR "according to dose" (≈);
CR of MBL was **inferior** to all the CRs of EM.

When testing ***associations*** in CRs in relation to EM, we found that:

CRs of both methods (PC and MBL) **weren't related** to any of the CRs of EM.

RESULTS

Patients` compliance categorization can be seen in Table 3. MBL resulted in the highest % of non-adherents. According to EM, 16.1% of patients were noncompliant to SRL.

Table 3 – Adherents/Non-adherents according to the methods used

Methods / Measures	PC	MBL	EM			CSR
			"according to dose"	"according to doses interval"	"according to days"	
Adherents	29 (93.5%)	Using CR: 3 (9.7%) Using mean levels: 18 (58.1%)	26 (83.9%)			29 (93.5%)
Non-adherents	2 (6.5%)	Using CR: 28 (90.3%) Using mean levels: 13 (41.9%)	5 (16.1%)			2 (6.5%)

When testing ***differences*** in patients` compliance categorization in relation to EM, we found that:

Adherents found with PC were **comparable** to those of EM;

Adherents found with MBL, *using CR*, were **inferior** to those of EM; *using mean levels*, they were ≈;

Adherents found with CSR were **comparable** to those of EM.

When testing ***associations*** in patients` compliance categorization in relation to EM, we found that:

Adherents/Non-adherents found with all methods (PC, MBL and CSR) **weren't related** to EM.

RESULTS

In CSR, besides self-reported noncompliance, pertinent information was gathered concerning noncompliant behaviour (Table 4 and Fig. 3).

Table 4 – CSR information on compliance determinants

	SRL (N=31)
Correct knowledge of study drug	24 (77.4%)
Very/somewhat good effect attributed to study drug	25 (80.6%)
First importance ranking attributed to study drug	27 (87.1%)
Attribution of problems specifically to study drug	3 (9.7%)
Compliance belief or motivational barriers	8 (25.8%)
Compliance recall (memory) barriers	4 (12.9%)
Compliance access barriers	0 (0.0%)

Compliance access barriers were not present (role of the free SRL provided by the pharmacy);

Most patients (61.3%) presented an ARS = 0.

Problems specifically attributed to SRL:
triglycerides/cholesterol increased levels & high sirolimus blood concentrations;

Compliance belief or motivational barriers were the most prevalent;

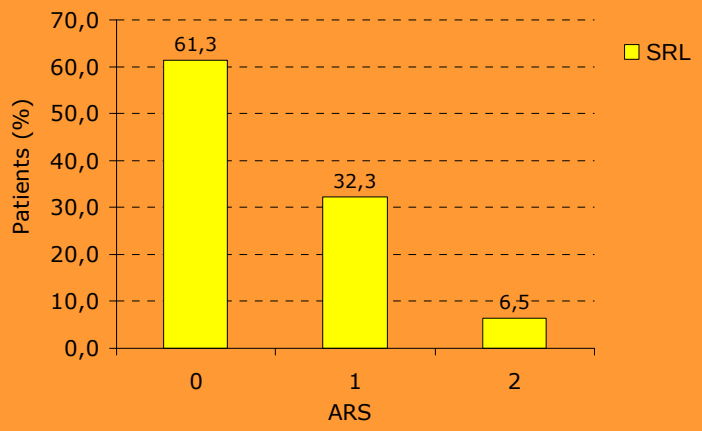

Fig. 3 – Distribution according to the nº of adherence risk factors present (Adherence Risk Scale – ARS)

RESULTS

We studied differences between adherents and non-adherents (EM-based), trying to generate hypothesis, to be further studied, about noncompliance risk factors (Fig. 4).

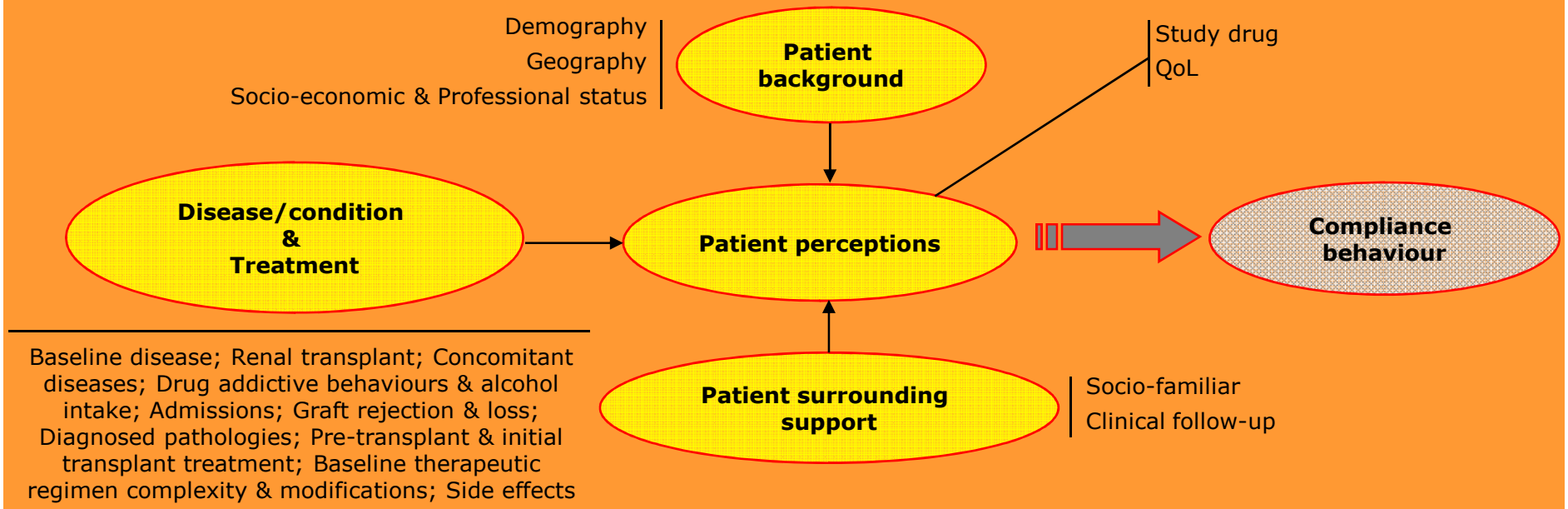

Fig. 4 – Studied potential noncompliance risk factors

RESULTS

Most of the studied risk factors wasn't related to noncompliance. Table 5 shows the few factors found to be associated [a) 1 socio-economic; and b) 2 condition/psychological factors, which have also been found by other authors (a) CHISHOLM, 2002; KAUL et al., 2000; and b) COCHAT et al., 2000; KAUL et al., 2000; WHO, 2003)].

Table 5 – Factors associated to noncompliance

FACTORS / GROUP		Patient background	Patient surrounding support	Disease/condition & Treatment		Patient perceptions
		Socio-economic & Professional status		Drug addictive behaviours	Alcohol intake	
SRL	N=31	Lower monthly net income *"per capita"* (p=0.002)	—	Presence of the behaviours (p=0.005)	Higher alcohol daily intake (p=0.003)	—

Conclusions are difficult to draw when we compare our data since, in general, other studies addressing this issue, including in the renal transplant population, are highly controversial in associating the vast majority of factors to the noncompliant behaviour.

Our results should be further investigated taking into account study limitations (e.g., short period of assessment, observational study, small sample size and weak statistical power).

DISCUSSION/CONCLUSIONS

- All invited patients accepted to participate in the study; sample size was limited by the available number of electronic monitors;
- We think that baseline characteristics of studied subjects were comparable to those of renal transplant patients, in general, and of patients of our centre, in particular;

- To minimize/overcome the methodological difficulties of compliance measurement:
  - Four compliance methods were used (1 direct; 3 indirect), as combination is the best way of measuring compliance, one being recognized as the closest to the “gold standard” - EM - that was used as reference;
  - We used compliance operational definitions according to the different methods, if clearly defined, and to investigators` criteria; to classify patients as adherents/non-adherents, we generally utilized the 80% CR “cut-off” level, the most widely used in literature;

- MBL was the method most exposed to bias (e.g., analytical methods, target levels, concentrations` nº and pharmacokinetics), and so yielded the least reliable results;

DISCUSSION/CONCLUSIONS

- When comparing results of EM with those of other methods we found no relations, and a strong trend to MBL under-estimate compliance, a weaker trend to PC over-estimate, and comparable results to CSR; different estimates are due to various methods/definitions, as shown in literature, confirming other authors' conclusions that measurements don't perform well in practice when tested against each others;
  - In spite of this, combination of methods can still be useful, according to study objectives and resources, as each one of them provides specific and complementary information (nevertheless, combination requires a model to reconcile differences);
- Considering EM, we found high CRs, probably due to the study design (prospective and "hawthorne effect"), drug profile and/or patients' fear of negative consequences of noncompliance (e.g., graft rejection/loss, leading to dialysis/re-transplantation); 16.1% were non-adherents, value inferior to those pointed out in general population (≈ 33.3%), similar to those for immunosuppressives in transplant patients (≈ 20%);

DISCUSSION/CONCLUSIONS

- Although study limitations, potential noncompliance risk factors evaluation tended to confirm that ***noncompliant behaviour is usually unpredictable*** (generally, the studied factors weren't associated to noncompliance; the few factors found to be related have already been mentioned in literature);
- A clear and trustworthy draw of conclusions about noncompliance risk factors can still not be made in face of all the controversy associated to the issue;

- More robust longitudinal and prospective studies (analytical/experimental) are needed, integrating the best suited methods to measure adherence, risk factors and clinical outcomes, all together, to accurately study medication noncompliance;

- Studies on compliance to immunosuppressives in renal transplant patients should contribute to a more rational and efficient graft allocation and/or maintenance.

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THANK YOU ALL
FOR
YOUR ATTENTION !