

# A RESEARCH NETWORK OF WALLOON PSYCHIATRISTS WORKING BOTH ON IN- AND OUT-PATIENTS FOR SPECIALISTS AND GENERAL PRACTITIONERS

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## ABSTRACT

The CIPUL ("Collectif d'Investigations Psychopharmacologiques à l'Université de Liège") groups psychiatrists specially sensitive to problems of clinical psychopharmacology. The homogeneity of the group results from their common formation at the Unit of Psychopharmacology (University of Liege) and allows a particular fidelity in diagnosis and clinical evaluation (rating scales).

The new psychotropic drugs (of which the hospital study can be done at the Unit of Psychopharmacology) can be tested 'on the ground' in the natural environment of the patient, which corresponds to the therapeutic reality of the psychiatrist and foreshadows the one of the general practitioner who is the principal prescriber of psychotropic drugs (especially anxiolytic, hypnotic and antidepressant drugs).

The psychotropic drugs that have been tested must comply with three main qualities : activity, tolerance, easy use.

The work group puts together the data of the investigation. The postulate is the equality of judgment between investigators well-balanced by quantity of handled cases. The group has a co-ordinator (J. Collard) who prepares the experimental design, collects results, analyses and writes the final report.

The results are rediffused for the general practitioners and the psychiatrists of the geographic area the University of Liege; then for international psychopharmacological information (CINP, ACNP).

## KEYWORDS

CIPUL; clinical investigation; clinical psychopharmacology; psychotropic drugs; antidepressants; methodology; evaluation.

## DEFINITION

The CIPUL ("Collectif d'Investigations Psychopharmacologiques à l'Université de Liège") is a group of psychiatrists from the University of Liege who undertake joint clinical trials with

psychotropic agents, both in hospitalized and ambulatory patients.

#### COMPOSITION

The CIPUL is a network of psychiatrists who are particularly sensitive to the problems of clinical psychopharmacology. On the one hand, the group finds its homogeneity in the common formation of its members at the 'Unit of Psychopharmacology' of the University Hospital, which allows a particularly high level of concordance where diagnoses, clinical evaluation and the use of rating scales are concerned. On the other hand, every member preserves his specificity : age, sex, former education (e.g. general practice), parallel training in other techniques (e.g. neurophysiology or statistics), type of activities (public service or private practice), locus of activity, type of patients (social levels, predominant pathologies).

#### STUDIES IN HOSPITALIZED AND AMBULATORY PATIENTS

One of the particularities of the CIPUL lays in that it performs studies in both out- and in-patients. Patients may be studied in one way only or in both ways for a complementary purpose.

##### a) Trials at the Unit of Psychopharmacology

The hospital studies are performed at the Unit of Psychopharmacology, a highly operational unit of twenty beds which is part of the General University Hospital. This environment or setting is particularly suitable for Phase I clinical studies : vicinity of other departments enabling a multidisciplinary approach (neurological, endocrinological, metabolic, toxicological, electrophysiological ...), high level of security with the possibility of rapidly obtaining biological tests and additional routine or advanced examinations, proximity of an Intensive Care Unit, large nursing staff trained for clinical evaluation, medical staff specially motivated for psychopharmacotherapeutic research where every physician has a specific role. This environment is particularly suitable for Phase I, princeps or pilot studies : e.g. lorazepam, 1971; flunitrazepam, 1972; or Phase II or III studies, versus placebo or versus a reference drug (e.g. toloxatone versus placebo, flunitrazepam versus nitrazepam). Phase I studies allow to check the activity of the drug, to evaluate the active dose, to verify the absence of toxicity and of major untoward effects. These studies involve a small number of carefully diagnosed and evaluated patients, and will be used as a criterion to determine whether the therapeutic benefit justifies further investigations. In Phases II and III, the control of the variables is possible in a setting of research well structured.

Hospital trials however present some inconveniences. On the one hand, they deal with patients with particularly severe or reluctant pathologies often needing high dosages; on the other hand, the patients who are not in their natural milieu, thus introducing bias or distortion (with a positive or a negative action). Furthermore, tolerance is appreciated very differently

by in- and out-patients (e.g. diurnal drowsiness). And the built-in placebo effect, common to every drug, differs in out- or in-conditions.

b) Trials in ambulatory patients

The ambulatory studies are closer to therapeutic reality. They concern the psychiatrist's usual patients who are treated in their natural environment. It is a naturalistic approach but different from the so-called 'Naturalistic Phase IV' from Overall. These out-trials involve other problems : e.g. the patients' compliance to therapy is decreasing and drop-outs or attritions often occur for unknown reasons. There is also the possibility of drug associations of which the investigator is not aware.

On the whole, the CIPUL thus operates in two major directions in evaluating psychotropic drugs: one 'intra muros', the other 'extra-muros', the latter being close to general practice.

TYPES OF PSYCHOTROPIC DRUGS UNDER EVALUATION

The CIPUL evaluations are mainly concerned with psychotropic drugs in the broad sense of the word (mainly anxiolytic, hypnotic, anti-depressant and neuroleptic drugs). Since a few years, its attention is particularly focused on antidepressants, where the existing medications are far from ideal profile :

- aleatory efficacy;
- onset of action rarely less than a week;
- presence of contra-indications;
- tolerance often poor (sedation, anticholinergic activity, anxiogenous effect);
- lethal risk (cardio-toxicity);
- complicated dosage scheme.

Therefore the CIPUL has undertaken evaluations of antidepressants :

- a) with different profiles : toloxatone versus placebo in hospital setting (deceiving results) and trazodone in out-patients (poor antidepressant activity);
- b) which are better tolerated : dothiepin appeared to be better tolerated than amitriptyline, although its activity is at least equivalent (out-patients);
- c) with sustained release, enabling a single daily intake thus improving patient's compliance :
  - the long-acting dibenzepine has shown a marked effect on vital drive and mood, as well as a higher anxiolytic activity;
  - the sustained release formulation of butriptyline did appear at least the equivalent to the classic formulation, but is better tolerated. In addition, it allows a simplified dosage scheme (thus enhancing patient's compliance), also improving sleep.

The CIPUL enables a better definition of the clinical profile of a psychotropic drug, viz. of tolerance and efficacy as well as of preferential indications. When compared to amitriptyline, pyritinol is not a traditional antidepressant; it appeared however to be a useful psychotonic drug in depressive syndromes (psycho-organic or not),

and its association with classic antidepressants is often beneficial: apparently it could be the optimal psychotonic compound. It can be compared with the studied pyrrisuccideanol which is an excellent anti-fatigue drug.

This kind of research field yields conditions which are close to the psychiatrist's clinical reality, foreshadowing that of the general practitioner who is the main prescriber of psychotropic drugs.

#### FUNCTIONING

The postulate is the equality of judgment of the members, balanced by the number of treated cases. The group includes a coordinator who thoroughly studies the preclinical files of interesting drugs, who selects them and draws up the experimental design which is then discussed by the participants. In order to isolate his own judgment, every member works alone and results are not divulged before a sufficient number of cases is gathered for evaluation. These results are then analysed and submitted to statistical analysis, often computerized, whereafter a final report with conclusions will be drawn up by the coordinator.

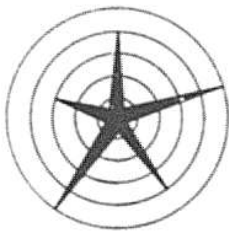
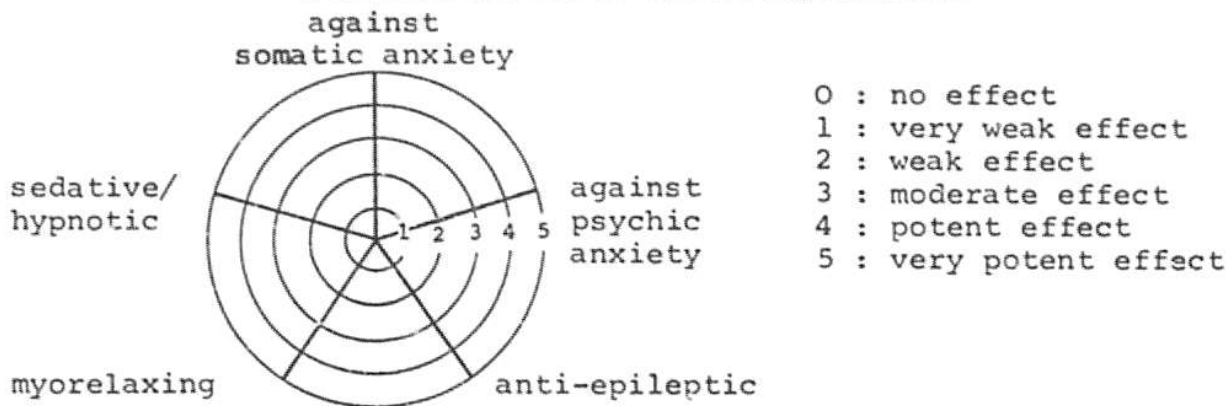
The CIPUL is a Walloon agency with an international vocation. Its results are diffused both to psychiatrists and general practitioners, first in the geographic area of the University of Liege. They are also destined for international psychopharmacologic information (CINP, ACNP). The CIPUL is under the patronage of the Director of Belgian Scientific Research (M. F. DETHIER).

To illustrate the task of information from the CIPUL towards the general practitioners, we propose a graphical representation of compared clinical activities of benzodiazepines marketed in Belgium. Five parameters are used :

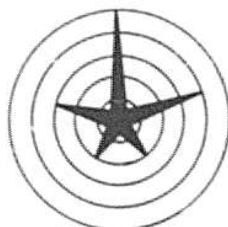
- 1) effect on anxiety ('psychic anxiety');
- 2) effect on fear ('somatic anxiety');
- 3) sedative/hypnotic effect;
- 4) effect on myorelaxation;
- 5) anti-epileptic effect.

As reference drugs we chose respectively diazepam (10 mg), lorazepam (2.5 mg), flunitrazepam (4 mg), diazepam (10 mg) and clonazepam (2 mg). We arbitrarily decided to represent the highest dosages available on the Belgian market. The graphical representation is based on the 'stars' from the School of Liege, which were already used for a representation of the clinical activity of neuroleptics. This voluntarily simplified representation of which some examples are shown, has essentially a didactic purpose; the graphical rating of the various benzodiazepines should help the practitioners to better adapt their prescriptions to the etiology and symptomatology of the patient's syndrom.

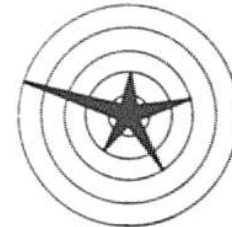




diazepam 10



lorazepam 2.5



flunitrazepam 4

The CIPUL arouses linguistic problems : it is French-speaking, which limits its enrolment possibilities : Dutch-speaking, German-speaking or immigrated patients (Italians, Spaniards, North-Africans ...) are thus kept off as rating scales are then not applicable (e.g. the French version of the M.M.P.I., computerized by M. DUFRASNE). Indeed, the range of validated French language scales corresponding to international rating scales is limited. In order to reach an international audience, the results must be published in English. This type of studies in a given population brings in transcultural problems on the methodological level; also maybe on the one of pharmacogenetics.

The methods which are currently used are based on interviews, subjective and impressionistic evaluation, and quantification scales. It can also resort to electrophysiologic (EEG - sometimes with N.C.V. -, EKG ...) or biologic methods. Computer, microinformatics, telematics are now introduced.

#### PROJECTS

With its actual structure, the research network agency named 'CIPUL' focuses on clinical evaluations of psychotropic drugs. This operating tool can be extended in several directions. On the one hand, to physicians who are not psychiatrists, particularly to general practitioners. They are in the best position to handle the second drug evaluation stage; one of the main reasons is that their patients often show a different psychic and environmental pattern. On the other hand to health co-workers, psychologists, sociologists, social workers ... in order to provide epidemiologic data from the Walloon population and thus to enable applications of social psychiatry or of transcultural evaluation with other research groups.

## CONCLUSIONS

Being a group of specialists, may the CIPUL or Collective for Psychopharmacological Investigations at the University of Liege take place in a Symposium which is dedicated to general practice ? It seems that the answer is yes. And for two main reasons :

- 1) the output of its research information goes essentially to general practice;
- 2) basically the CIPUL consists of an 'inner circle' of psychiatrists, but it is our intention to complete it with an 'outer circle' of general practitioners supplying it with additional clinical data and evaluations based on a larger patient sample, therefore to get closer to daily therapeutic reality.

In our opinion, the best approach is a closer cooperation between specialists and general practitioners.

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## REFERENCES

- Ansseau, M. et St. Diricq (1979). Les benzodiazépines. The Upjohn Medical Monographs, 1 (10), 1-38.
- Collard, J. (1971). Initial psychopharmacological study of lorazepam (WY 4036). Arzneim. Forsch., 21, 1091-1095.
- Collard, J. (1972). Le contrôle de l'insomnie par une nouvelle benzodiazépine : le flunitrazepam ou Ro 5-4200 (investigations princeps de phase I et contrôlée de phase II). Acta Psychiatr. Belg., 72, 721-735.
- Collard, J. (1973). Méthodologie en Psychopharmacologie Clinique. Masson, Paris.
- Collard, J., St. Diricq and M. Ansseau (1979). A comparative controlled clinical study of butriptyline ('Evadyne'), in standard and sustained-release formulations, in the treatment of depression. Pharmatherapeutica, 2, 260-264.
- Collard, J., M. Dufrasne, J. Fraipont, Fr. Couteaux et A.M. Lamboray (1978). Un nouvel agent antidépressif : la dothiepin. Rev. Méd. Liège, 33, 275-279.
- Collard, J., J. Fraipont and M. Dufrasne (1973). The first long-acting ('retard') thymoanaleptic or antidepressant : the time-released dibenzepine with prolonged action. Arzneim. Forsch., 23, 537-545.
- Collard, J., J. Fraipont, Ph. Schouteden et St. Diricq (1977). Pyritinol et antidépresseurs. In M. Van den Berghe et R. De Buck (Ed.), Hypométabolisme cérébral, European Press, Gent, pp 70-84.
- Collard, J. et M. Dufrasne (1979). De l'intérêt de l'ordinateur pour l'étude par M.M.P.I. d'un psychotrope : le tiapride. Psychol. Méd., 11, 763-769.