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Drug-prescription Management in Patients with Multiple Chronic Conditions

Results of the experimental Polychrome study

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In a context where the prevalence of chronic diseases is constantly rising, drug-related risks confronting patients suffering from multiple chronic conditions (MCC) remains poorly documented. Although certain undesirable adverse effects are inherent to the use of a drug and therefore inevitable, certain adverse effects could be prevented as they result from non-compliance with indications and recommendations.

The experimental Polychrome study provides some answers. On the one hand, it reveals that the treatment of MCC patients is a predominant aspect of general medicine and inevitably results in polypharmacy (multiple drug prescriptions) and, on the other, that the concurrent use of multiple drugs is not without iatrogenic risk. Serious adverse drug reactions are nevertheless relatively rare. More generally, the study reveals that drug prescription quality could be improved; notably by reducing prescription imprecisions and inappropriate dosage, but equally in reducing the number of drugs prescribed.

If the Polychrome study remains experimental, it nevertheless reveals the difficulties facing general practitioners in prescribing drug treatments for MCC patients. It also provides interesting perspectives for the optimal use of pharmaceutical drugs and their use in combination with alternative, drug-free therapies.

A pharmaceutical drug is an active substance whose use must necessarily involve weighing health benefits (improved health status) against potential risks. Known as drug-induced illness (iatrogenesis), certain risks are inevitable as they are inherent to using drugs whereas others result from non-compliance to indications or recommendations (specified in the marketing authorisations) and could be prevented. In this case one refers to drug-drug interactions or drug-disease contraindications (Definitions insert).

Even though serious adverse effects are extremely rare[1], pharmaceutical drugs are responsible for a number of hospital admissions: approximately 3 to 4% of hospital admissions are due to adverse reactions to medication, half of which could have been prevented (Imbs *et al.*, 1999; Pouyanne *et al.*, 2000 ; Michel *et al.*, 2005; Affssaps, 2008).

If the relationship between multiple chronic conditions and polypharmacy is recognized among the elderly, notably the higher associated risk of adverse drug reactions (Sermet, 2002), the risks associated with using drug-based therapies

[1] An emblematic example is thalidomide, prescribed to pregnant women in the 1950's against nausea that provoked serious foetal malformations and was withdrawn from the market in 1961.

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throughout the life of a MCC patient is poorly documented. Yet, as we have observed from data obtained from the 2008 Health, Health Care and Insurance survey (ESPS), MCC and polypharmacy are two correlated phenomena that occur well before the age of 65 (graph 1).

According to the ESPS 2008 survey, over four out of ten individuals aged 16 and over suffer from multiple chronic diseases. With the increasing prevalence of chronic diseases and associated drug treatments prescribed increasingly early, the combined management of MCC and polypharmacy provides a new challenge not only for public health policy but also in terms of cost control. Compared with other European countries, France effectively continues to take the lead in average drug expenditures per capita (Sabban et Courtois, 2007).

Health professionals' expectations are equally high concerning the development of optimal strategies aimed at improving drug prescription quality and greater developments in the use of alternative drug-free therapies. First contact care, historically focused on treating acute disorders, is now on the front line in the overall care of MCC patients.

The aim of the experimental Polychrome study was to evaluate the incidence of polypharmacy among MCC patients and to determine whether a multidisciplinary medical team was able to propose an optimisation programme to improve the quality of prescriptions.

Polychrome: an experimental study on GP drug prescriptions for MCC patients

The Polychrome project was developed in three main phases (diagram 1 and Methods insert).

The first quantitative phase was aimed at measuring the percentage of MCC patients from a sample of GP patient lists, classifying them by age, gender and clinical condition and in parallel, documenting the characteristics of their drug treatments.

The typology resulted in the partition of MCC patients into six classes. Four of the classes, made up of patients aged 40 and over, formed the basis for the second, qualitative phase of the project. Supported by two teams of experts (pharmacologists and clinicians), the second phase involved the analysis of two drug prescription sub-samples to evaluate the potential risks of iatrogenesis and suggest ways of optimizing the prescriptions.

The third qualitative phase of the Polychrome project was aimed at analysing the determinants of polypharmacy using focus group sessions involving 60 general practitioners, of which half were members of the French Society of General Medicine (SFMG).

Background

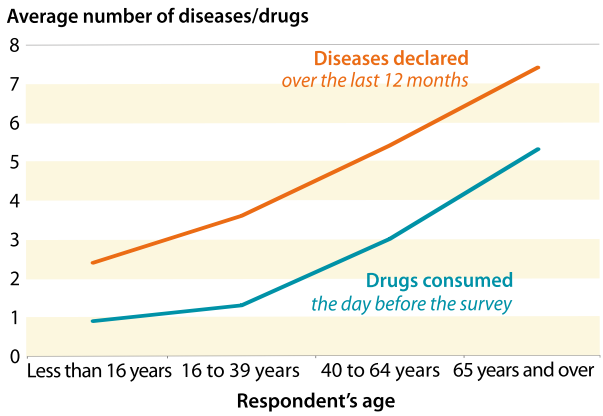
The Polychrome study was elaborated and piloted by Pascal Clerc within the framework of a multidisciplinary and multi-institutional partnership. IRDES participation consisted in providing methodological assistance in creating the research protocol, its implementation and the dissemination of the results. This collaboration fits within the framework of IRDES continuing research on the analysis of the medical decision among GPs. The project was financed by the Cnamts, MGEN (a French mutual benefit insurance company "*mutuelle*") and the French National Health Autority (HAS).

Serious adverse drug reactions are relatively rare

According to the team of pharmacology experts[2], who assessed the potential iatrogenic risks in the 105 randomly selected drug prescriptions, almost two thirds presented at least one drug-related contraindication and/or interaction (table 1). The vast majority of drug-disease contraindications are related to cardiovascular or respiratory system disorders and the majority of drug-drug interactions from drugs prescribed for cardiovascular or nervous system disorders.

[2] Annie Fourrier-Réglat and Françoise Haramburu (Pharmacoepidemiological Unit and the Pharmacosurveillance Unit, Bordeaux Pharmacology Department), and Virginie Boyer (Inserm U 657 – *Pharmaco-épidémiologie et évaluation de l'impact des produits de santé sur les populations*).

G1 Number of diseases and drugs, according to the age of individuals declaring at least one chronic disease



Data: Health, Health Care and Insurance Survey 2008.

T1 Analysis of prescriptions with contraindications or drug-drug interactions

	Pharmacology experts						
	Total	with disease/drug contraindications			with drug-drug interactions		
		Number	%	... absolutes	Number	%	... unadvisable
Prescriptions/patients/visits	105	60	57%		70	67%	
Diseases	528	154	29%				
Specific diseases	72	26	36%				
Drugs	676	154	23%	2.80%	394	58%	3.25%
Different drugs	97	25	26%		45	46%	

Reading guide: The disease-drug contraindications, present in 57% of the 105 prescriptions/patients/visits, are concentrated in one third of the diseases (29%). Drug interactions, present in 67% of the 105 prescriptions/patients/visits, are more dispersed since they concern over half (58%) the drugs prescribed.

Data: Polychrome Project.

Potentially serious contraindications or interactions are nevertheless rare (6% of prescriptions). Formal contraindications essentially concern the cardiovascular system (for example a beta blocker prescribed to a patient with arteritis, or a benzodiazepine to a patient with respiratory failure) and the same applies to unadvisable drug-drug interactions (for example a beta blocker associated with a calcic inhibitor).

Drug prescriptions that could be optimised

A second team of experts composed of 6 doctors and a pharmacologist proposed the optimisation of 11 prescriptions among the 16 'archetypal' drug prescriptions selected for expert assessment.

For each of the prescriptions, an optimality score was calculated as the ratio between the drugs considered of clinical interest by the experts and the total number of drugs itemised on the prescription (Methods insert). The average overall optimality score for the 11 prescriptions was 58% and varied from 22 to 100% (table 2).

The experts then attempted to optimize the prescriptions even further. The detailed analysis of the optimisation process shows that the experts modified 80% of drugs itemised on the prescriptions analysed (graph 2), 20% remaining unchanged. Modifications either involved stopping a treatment, substituting one drug for another or a non-pharmaceutical alternative, or in the majority of cases modifying the prescription contents.

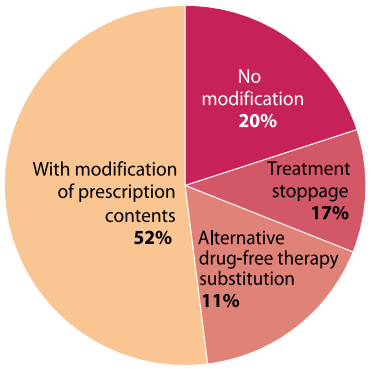
Drug stoppage was recommended in 17% of cases and essentially motivated by unclear therapeutic indication, discontinued or withdrawn marketing authorizations, insufficient effectiveness, or inappropriate prescription duration.

Replacing drug treatments by alternative drug-free therapies was recommended in 11% of cases. For example, alternative treatments for rheumatic pain included dynamic therapy (walking, walking stick), infiltrations (corticoids or visco-supplementation) or consulting a paramedical professional (physiotherapist, ergotherapist).

The greatest number of modifications (52%), however, concern altering the prescription 'instructions' because of imprecision concerning the distribution of drugs over a 24 hour period or inappropriate dosage, either too high (e.g. benzodiazpines, proton pump inhibitors) or too low (e.g. statins, paracetamol).

Founded above all on clinical criteria, the optimisation process had a pharmacological impact since the number of prescribed drugs was reduced by 30%. More particularly, the number of contraindications decreased by 46% even though there remained an absolute contraindication (metformine combined with heart failure) and drug interactions decreased by 66%; all unadvisable drug combinations were eliminated.

G2 **Modifications associated with the optimisation of drug prescriptions**



Data: Polychrome Project.

The point of view of general practitioners: the complexity of causes underlying polypharmacy

Focus groups conducted among 60 general practitioners (Methods insert) permitted the study of drug prescription determinants in the context of MCC. An analysis of the comments and contextual

T2 **Characteristics of the 11 prescriptions analysed by the group of expert clinicians before and after the optimisation process**

				Before optimisation			After optimisation				
No	Gender of patient	Age of patient	Number of diseases	Number of drugs	Number of contrain-dications	Number of drug-drug interactions	Optimality score	Number of drugs	Prescription difference (%)	Contrain-dications	Drug-drug interactions
1	Male	44	3	6	0	1	50%	4	-33%	0	0
2	Female	78	7	7	2	1	86%	5	-29%	1	0
3	Male	83	9	12	10	2	58%	9	-25%	0	0
4	Female	71	9	9	1	1	56%	6	-33%	0	0
5	Female	81	13	13	9	7	54%	9	-31%	0	0
6	Male	79	9	10	6	5	70%	10	0%	5	3
7	Female	77	4	8	2	7	38%	4	-50%	0	0
8	Male	57	7	9	3	4	22%	4	-56%	0	0
9	Female	77	7	10	2	2	100%	8	-20%	0	0
10	Male	79	10	12	3	2	42%	7	-42%	0	0
11	Male	78	10	9	0	3	78%	8	-11%	0	0
		Total	**88**	**105**	**38**	**35**	**58%**	**74**	**-30%**	**6**	**3**

Note: The optimality score for each prescription is the ratio between the number of itemised drugs considered of clinical or immediate interest and the total number of drugs itemised on the prescription.

All the contraindications and drug interactions are included, not just the four unadvisable 'serious' cases (absolute contraindications or drug interactions). After optimisation, all the unadvisable drug interactions were eliminated and only one absolute contraindication remained.

Data: Polychrome Project.

representations forwarded by participating GPs underlines the complexity of causes leading to polypharmacy[3].

Factors leading to polypharmacy can be grouped into three main types:
- factors relative to the patient and doctor-patient interactions (MCC, behaviours and representations),
- factors relative to the GP (medical decision-making process, coordination/communication with specialists, internal organization of the medical practice),
- factors influencing GP or patient behaviours.

Polypharmacy is above all related to MCC

The GPs reiterate that MCC is the principle factor determining polypharmacy.

This situation can be aggravated by an accumulation of medical recommendations in that each condition is invariably treated separately which consequently leads to multiple drug prescriptions depending on the number of risk factors or the severity of the disease (for example, three different drugs can be prescribed to equilibrate a type 2 diabetes or high blood pressure). An additional factor adds to the confusion: the multiple sources of information addressed at GPs (the French National Authority for Health, medical expert societies, the National Health Insurance Fund for Salaried Workers, the pharmaceutical industry, the French Agency for the Safety of Health Products…).

'I think that thirty years ago (…), we were seeing a large number of cases of rhinopharyngitis, but there was a great deal less prevention than today (…) When we treat a case of hyperlipidemia, diabetes or high blood pressure it falls into the domain of preventive medicine'

Patient behaviours that encourage polypharmacy

The importance of the quality of the doctor-patient relationship was emphasised. The GP's motivation in fighting against the facility of writing out a prescription depends on the relationship with the patient and the latter's own implication in the treatment. GPs feel confronted with patient refusals to alter existing therapies (reducing pharmacologic prescriptions or alternative drug-free proposals), or under 'pressure' to prescribe. Patients primarily expect to be relieved of pain or anxiety in a societal context highly focused on medication which

'I'm thinking of prescriptions in cases of hypercholesterolemia and hyperlipidemia for example. When we have an alternative other than medication to treat a condition, for example dietetics, and the patient refuses to accept it. We are sometimes constrained to prescribe a drug. Personally, I don't necessarily find this satisfactory.'

[3] This work is the subject of a medical thesis at the Kremlin-Bicetre Faculty.

Method

The qualitative analyses of drug prescriptions

Each drug prescribed on the 105 randomly selected prescriptions was first analysed by pharmacological experts in terms of potential drug-drug interactions (figuring on the same prescription) and drug-disease contraindications. The interactions and contraindications were determined from the Vidal 3 electronic thesaurus. Recommendations or alternative solutions were not provided following the identification of problems caused by the adverse effects of the prescriptions.
In the second phase, each member of a multidisciplinary team designated to optimize prescriptions comprised of a GP, a cardiologist, an endocrinologist, a psychiatrist, two geriatricians (one of which was originally trained in rheumatology) and a pharmacologist were asked to individually evaluate the appropriateness of 16 typical prescriptions using the Medication Appropriateness Index (MAI) below, and eventually make recommendations to modify the prescription.

Medication Appropriateness Index criteria

Therapeutic indication - Effectiveness (medical service rendered) - Dosage – Distribution over 24 hours - Prescription duration - Practical Utilisation - Contraindications - Drug-drug Interactions – Drug used for adverse effect - Drug duplication - Drug omission.

The experts were then reunited for a whole day to carry out the analysis and give their final proposals concerning the 16 typical case prescriptions. For each typical case studied, the procedure was as follows:

1. Judgement on the clinical interest and appropriateness of each item for each prescription according to a scale of 4 criteria (Denneboom et al., 2006) resulting in an optimality classification for each prescription. It is defined as the ratio between the number of drugs considered by the experts as having a clinical interest and the total number of drugs itemised on the prescription (table 2).

2. Proposals for the modification of non-optimal prescriptions. The prescription adjustment process was effectuated following a step-by-step procedure analysing diagnostic justifications, dosage, the distribution of drugs over a 24hr period, the elimination of duplicate drugs and medication for the adverse effects of unjustified medication. Simultaneously, the practical aspects relating to the feasibility of the proposed modifications and their clinical interest were taken into account. A consensus of opinion was not obligatory and several prescription proposals were accepted, as were proposals for clinical monitoring and/or alternative, non-pharmacological proposals.

The GP focus groups

The recruitment of 60 general practitioners from the French Society of General Medicine (SFMG) file constituted of 8,000 general practitioners belonging or not to the learned society was based on three criteria:
1. half the group were not to be SFMG members,
2. their distribution by age and type should correspond to that established by the National Council of the Order of Physicians (Conseil national de l'Ordre des médecins (Cnom)),
3. their distribution by practice territory should be close to that of France as a whole.

The 60 general practitioners were divided into ten groups. Two separate days were necessary to record all the sessions. The groups were steered by 5 experienced professionals and guidelines were elaborated. Each day involved four work sessions each lasting 1hr 30 m.

An initial session was devoted to 'brain-storming' on prescription optimisation based on the following questions:

1. In your opinion, what is a non-optimal prescription?

2. Do you think that certain of your multiple drug prescriptions are not optimal? If yes, why? (With examples of patients that spring to mind).

3. Why do you think that certain prescriptions cannot be optimized? How do you manage them? (With examples of patients that spring to mind).

The three following work sessions were organised around the16 typical case prescriptions analyses by the experts. The group discussion followed a step-by-step development around 3 questions:

1. What do you think of this prescription? Do you have identical types of prescriptions and if so, for what type of patient?

2. How would you have optimized it?

3. For what reasons would it not be possible to optimize this prescription?

50 hours of audio recordings were collected and transcribed by a professional. The contents analysis was carried out by three researchers using the Nvivo 8 analysis software. Several meetings were held to standardise coding.

subsequently influences their representations of illness and medication.

A complex medical decision-making process that is not entirely governed by clinical factors

GPs highlight numerous reasons leading to polypharmacy that have their origins in the context in which the medical decision is taken or the complexity of the decision-making process. The contextual and organisational factors put forward by GPs underline the difficulty coordinating and communicating with specialists, the accumulation of recommendations focusing on a particular problem for MCC patients and finally, the medical practice's internal organisation including the daily workload distribution between patients suffering from acute disorders and chronic illnesses.

'In fact, coordination is time-consuming. If you have a problem concerning two different drugs and you need to contact a specialist, you're going to waste half an hour on the telephone. Easily, and in an environment where you don't necessarily have half an hour to spare on that kind of issue'.

The second factor is related to GP preferences and personal beliefs, themselves influenced by other factors (training, sensitivity to health issues, contacts with sales representatives from the pharmaceutical industry), as well as their personal motivations towards the patient.

'(...) Even if we always deny being influenced by industry, there was perhaps a time when we would have regularly prescribed Asasantine[4] because it had been presented to us. Now, no-one knows what it is anymore because it's no longer presented. We often find ourselves saying: "I used to prescribe that in the past". 'But I nevertheless deny being influenced by the pharmaceutical industry. I think that the industry's message has an influence whether conscious or unconscious'.

D1

Polychrome study

1st PHASE: Selection of general practitioners, patients and consultations

Constitution of the sample

Time-period: 2002-2004
Base: Observatory of General Medicine (OMG) and the French Society of General Medicine (Société française de médecine générale: SFMG)
Patient selection criteria: at least one chronic disorder during the years 2002 and 2003, with at least one session for 2002,2003 and 2004.
Sample: 68 GPs, 45,018 patients, 284,216 sessions (consultations and visits), 718,772 pathologies, 1,471,678 drugs.

Construction of the typology

Typology of MCC patients

Class 1	Class 2	Class 3	Class 4	Class 5	Class 6
Proportion of MCC patients in the patient list					
37.80%	23.14%	14.34%	13.34%	7.52%	3.83%
Summary Class Heading					
Cardiovascular (risk factor and complications) and rheumatology among patients aged 60 and over	Broad ranging disorders among women aged 70 and over	Psychiatry and muscular-skeletal disorders in patients aged below 60	Cardiovascular risk factors and muscular-skeletal disorders in patients aged 40-69 years old	Dermatology, asthma and rhinitis, and muscular-skeletal disorders in patients aged 11-25 and 40-59	Anxiety and muscular-skeletal disorders in 11-39 years olds
Example of associated chronic disorders					
High blood pressure combined with hyperlipidemia and coronary disease	Osteoarthritis combined with varicose veins and coronary disease	Lumbago combined with depression, neck pain and insomnia	High blood pressure combined with hyperlipidemia and diabetes	Rhinitis combined with asthma,	Lumbago combined with anxiety
Example of drug associations					
Converting enzyme inhibitor associated with a cholesterol-lowering drug, beta-blocker and antithrombotic drug	Level I or II analgesic associated with a venous vasodilator, beta-blocker and antithrombotic druge	Non-steroid anti-inflammatory drugs associated with an analgesic, anti-depressant and a centrally acting myorelaxant	Beta-blocker associated with a cholesterol-lowering drug and an oral anti-diabetic drug	Systemic antihistamine associated with inhaled andrenergic bronchodilator, topical corticosteroids	An anxiolytic associated with a non-steroid anti-inflammatory drug and an analgesic

2nd PHASE: Analyses

Sample: patients from class 1 to 4.

105 prescriptions are **randomly selected according to typology class**. Are identified: patient gender and age, number of consultations per year, the patient's diseases and corresponding prescription (drugs and dosage). The field covers 105 patients/consultations, 53 GPs, 528 diseases and 676 drugss.

Evaluation of the potential risk of contraindications and drug-drug interactions in selected prescriptions
by experts in pharmacology

Among these, 16 prescriptions were **selected for their 'archetypal' nature** in terms of MMC and polypharmacy but only 11 prescriptions were analysed, that is to say 11 patients/consultations, 88 diseases and 105 drugs.

Optimisation of prescriptions (polypharmacy)
Carried out by a group of experts made up of clinicians and one pharmacologist

3rd PHASE: General practitioner focus groups

Constitution of the sample
- 30 members of the SFMG
- 30 non-members of the SFMG

Analysis of polypharmacy determinants

The third factor relates to diagnostic uncertainty due to the historical documentation of a symptom or clinical diagnosis. This is all the more valid for 'inherited' diagnoses when a patient changes GP. The failure to re-evaluate previous diagnoses that have been under or overestimated often induces errors of judgement and consequently inappropriate prescriptions.

Finally, GPs also shed light on the decision to prescribe drugs, the routine of choosing an easy option or through therapeutic inertia (renewal of an existing drug prescription, the patient's attachment). In this context, for a long-term stabilised MCC patient, the pres-

[4] Drug indicated in the prevention of cardiovascular accident within a three month period after a transient ischemic attack related to artheroscleroris.

cription is automatically renewed without asking questions.

* * *

'She said she had been suffering from headaches for years and years and that they started at the age of 20. I had never seen her in a headache crisis, she had never had a headache crisis and I thought, 'Why keep her on this drug? Taking it all the time with its potential side-effects…' So despite that fact that she had never had a crisis, she clung on and clung on.'

The experimental Polychrome project, by associating a quantitative and qualitative approach with experts in pharmacology and clinicians, prepared the ground for a field of research little explored in France.

In the first place, MCC patients form an essential part of a GPs' activity and inevitably leads to the polypharmacy phenomenon. Secondly, multiple drug prescriptions are not without iatrogenic risk even though serious adverse reactions are relatively rare. If the possibility of reducing this risk exists, it is impossible to eradicate completely. These potential 'anomalies' highlight GPs difficulties in treating MCC patients with multiple medications.

Polypharmacy is the result of numerous causes. It is not only the product of patient characteristics, behaviours and representations but also of GP beliefs and preferences, doctor-patient interactions, and occasionally more systemic or organisational factors: coordination between GPs and specialists, relationships with the pharmaceutical industry, work time management, clinical recommendations.

This experimental study, however, has its limits: even if the drug prescriptions studied were archetypal and emblematic of numerous clinical situations, their number was limited. In addition, the pharmacological experts' evaluation and prescription optimisation was effectuated without the presence of the patient, without the possibility of consulting the patient's medical file for additional data, and without access to the prescriber's reasoning. Finally, this procedure cannot be generalised because of the cost involved.

The Polychrome project nevertheless provides interesting perspectives for the optimal use of pharmaceutical drugs and their use in combination with alternative drug-free therapies that can be addressed at several levels: to learned societies and prescribers by indicating basic elements that can optimise a prescription; to learned societies in general medicine and other medical specialities by inviting them to participate in combined work sessions (with cardiologists, rheumatologists, psychiatrists, geriatricians…); to the health authorities (French National Health Authority, French Agency for the Safety of Health Products) for a global approach to MCC with operational pharmacological and pathological references; to the patients by improving their access to information on drugs and increasing their awareness of alternative, drug-free therapies; to researchers in inciting them to work on the economic repercussions of polypharmacy and associated iatrogenic risks. ♦

Definitions

Patient with multiple chronic conditions

Patient with at least two coexisting chronic disorders. Disease chronicity was defined on the basis of three criteria by eight experts participating in the Observatory of General Medicine: recurrent consultations, spread over a long period of time (at least two contacts per year for three consecutive years), and serious repercussions on the patients' quality of life.

Iatrogenic risks

- A drug-disease contraindication, is a physical or more often physiological factor that formally opposes the prescription of a given drug even if the patient equally presents an indication for which the drug is recommended.
- Drug-drug interaction describes the qualitative or quantitative modification of a given drug's effects following the simultaneous (or successive) administration of one or several other drugs (or active substances such as food, alcohol…).

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Glossary

- **Adverse drug reaction:** effet indésirable médicamenteux
- **Drug-disease contraindication:** contre indication pathologie-médicament
- **(Drug-)drug interaction:** interaction médicamenteuse
- **Drug-induced illness:** effet indésirable médicamenteux
- **Latrogenic risk:** risque iatrogénique
- **Polypharmacy:** polyprescription
- **Undesirable adverse effect:** effet indésirable

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