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Polypharmacy: Definitions, Measurement and Stakes Involved Review of the Literature and Measurement Tests

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Polypharmacy, defined by the World Health Organisation as "the administration of many drugs at the same time or the administration of an excessive number of drugs" is frequent among the elderly as they often suffer from chronic diseases with concomitant pathologies. If polypharmacy is legitimate in some cases, it can also be inappropriate and in all cases carries the risk of adverse effects or drug interactions. In an ageing society such as ours, polypharmacy is a major public health issue in terms of quality and efficiency of care and health expenditures. It is thus essential to examine the definitions and measurement of polypharmacy.

Based on a review of the literature, different definitions of polypharmacy were identified (simultaneous, cumulative and continuous polypharmacy) and the measurement of polypharmacy was examined according to different thresholds. The five most frequently used tools to measure polypharmacy, according to the literature, were then tested using the IMS Health database, Disease Analyzer on 69,324 patients and 687 physicians. The aim was to compare the ability of indicators to identify polypharmacy and to evaluate the technical feasibility of their calculations.

olypharmacy is defined by the World Health Organisation as "the administration of many drugs at the same time or the administration of an excessive number of drugs" (WHO, 2004). Habitual and often legitimate among elderly patients, it is considered appropriate or legitimate in cases of

concomitant pathologies or in complex medical situations in which prescribed medications respect recommendations. Inversely, it becomes problematic when one or more medications are inappropriately prescribed or when the anticipated benefit for the patient is not obtained (Duerden *et al.*, 2013). In any case, the

ageing of the population and the risks of iatrogenesis¹ means that polypharmacy is

latrogenesis covers all adverse health effects caused by medical practices or drugs prescribed by health professionals with the aim of maintaining, improving or restoring health (Garros, 1998).



a major issue in terms of quality of health and the appropriateness of prescribing.

Polypharmacy: an economic and public health issue

Overuse of medication carries major health risks, especially among the elderly. There is a significant link between polypharmacy and the emergence of adverse effects, drug interactions, falls and even increased mortality (Field et al., 2001; Field et al., 2004; Frazier, 2005; Neutel et al., 2002; Jyrkka et al., 2009b). Each new specialty administered increases the risk of adverse effects by 12% to 18% (Calderon-Larranaga et al., 2012). These iatrogenic accidents are responsible for 5 to 25% of hospital admissions and 10% of emergency admissions (Pirmohamed et al., 2004; Hohl et al., 2001; Lazarou et al., 1998). Polypharmacy is a predictive factor in terms of hospital stay duration, mortality and hospital readmissions (Campbell et al., 2004; Frazier 2005; Sehgal et al., 2013). It creates problems of compliance when the dosing regimen is too complex (Bedell et al., 2000). Finally, polypharmacy significantly increases the risk of potentially inappropriate prescribing with debatable indications and a risk of adverse effects or inefficiency (O'Mahony and Gallagher, 2008; Hanlon et al., 2001; Cahir et al., 2010; Pugh et al., 2006; Carey et al., 2008; Bourgeois et al., 2010b).

Polypharmacy is more and more frequent. In the United States, the number of medical consultations with elderly patients resulting in 5 or more prescribed drugs increased from 6.7% to 18.7% between 1990 and 2000 (Aparasu *et al.*, 2005). Similar trends have been observed in Sweden with a 15% increase in polypharmacy (10 medications or over) between 2005 and 2008, and in New Zealand where it increased from 1.3 to 2.1% from 2005 to 2013 (Nishtala and Salahudeen, 2014; Hovstadius *et al.*, 2010).

The elderly population is the most affected by polypharmacy and its consequences. The increase in the prevalence of agerelated chronic diseases is accompanied by an increase in medications (Clerc *et al.*, 2010). The elderly are more often exposed

to the risks of iatrogenesis as, with age, they are subject to physiological changes in their metabolism and can have difficulty following a complex treatment regimen due to a decline in their cognitive abilities (Corsonello *et al.*, 2010).

These prescription quality issues are coupled with economic issues. Other than the additional costs incurred by the consumption of useless, dangerous or inappropriate medications, the number of hospitalisations due to iatrogenic accidents and treatment intensification generated by adverse effects contribute to increasing expenditures related to polypharmacy and reduces the efficiency of care (Hovstadius and Petersson, 2013).

Improving the quality and efficiency of drug prescriptions among elderly patients has been an ongoing concern in France for a number of years. Within the framework of the 'National Ageing Well 2007-2009² plan ("Bien vieillir 2007-2009"), the High Authority for Health (Haute Autorité de Santé, HAS) developed the "Drug Prescription among Aged Subjects" ("Prescription médicamenteuse chez le sujet âgé") pilot scheme aimed at disseminating tools to improve prescribing practices, notably with regard to polypharmacy, and to better control the risks of iatrogenesis (HAS, 20133). In December 2013, the report on drug management policy in homes for elderly dependent persons (Etablissements d'hébergement pour personnes âgées dépendantes, EHPAD) [Verger, 2013] underlined the frequency of polypharmacy and proposed measures to improve the use of medication. The experimental program "Seniors Health Path" ("Parcours santé des aînés" (PAERPA)) also proposes therapeutic education actions⁴ regarding polypharmacy and comorbidity. In order to monitor the effects of these



This article fits within the framework of research conducted by IRDES on the quality and efficiency of drug prescriptions. The focus on polypharmacy has a dual aim: to define and test an appropriate polypharmacy indicator that can be used in follow-on research on the subject and to contribute to reflexions on the indicators used to evaluate the Seniors Health Path program ("Parcours santé des aînés", Paerpa).

programs, reliable indicators that are easily replicated routinely are necessary.

Which indicators to measure polypharmacy? A review of the literature

The first phase of this research questioned the definition of polypharmacy and its measurement. A review of the literature served as a base from which to identify the different approaches to polypharmacy: simultaneous, cumulative, continuous... The medication threshold defining the existence of polypharmacy was also examined. Finally, the aims, scope of application, methods of construction and useable databases were specified for each indicator.

In the second phase, five tools measuring polypharmacy were tested on the IMS Health prescriptions database "Disease Analyzer" (Becher *et al.*, 2009) so as to compare the capacity of the selected indicators to identify polypharmacy and to evaluate the technical feasibility of their calculations.

Bibliographical research strategy

The review of the literature was carried out using the Medline and Gediweb databases (2000-2013) and completed with research based on references included in selected articles. The following key words were used to designate polypharmacy: "polypharmacy", "polymedication", "polyprescription", "multimedication", "multiprescription". In total, 655 articles or documents were identified.

National Ageing Well Plan 2007-2009 – Plan National Bien Vieillir: http://travail-emploi.gouv.fr/ IMG/pdf/presentation_plan-3.pdf

³ HAS plenary session: Drug prescription among elderly subjects – latrogenesis prevention – Professional plateform – Warning and control indicators - Saint-Denis, November 29th 2012; www.has-sante.fr/portail/jcms/c_1637256/fr/ pleniere-has-prescription-medicamenteusechez-le-sujet-age-prevention-de-la-iatrogenieplateforme-professionnelle-indicateurs-dalerteet-de-maitrise-saint-denis-29-novembre-2012

FTP reference framework/Paerpa http://www.has-sante.fr/portail/upload/docs/ application/pdf/2014-09/cadre_referentiel_etp_ paerpa__polypathologie.pdf

Following a reading of article titles and abstracts by two independent readers, 53 articles answering the following inclusion criteria were retained: articles or literature reviews on the definition and measurement of polypharmacy, studies on the prevalence of polypharmacy (excluding polypharmacy centered on a single therapeutic class or pathology) and articles in French or in English. After reading the references included in these articles, a further 11 articles were selected. After reading, a total of 34 articles were retained for the review of the literature.

Polypharmacy can be simultaneous, cumulative or continuous

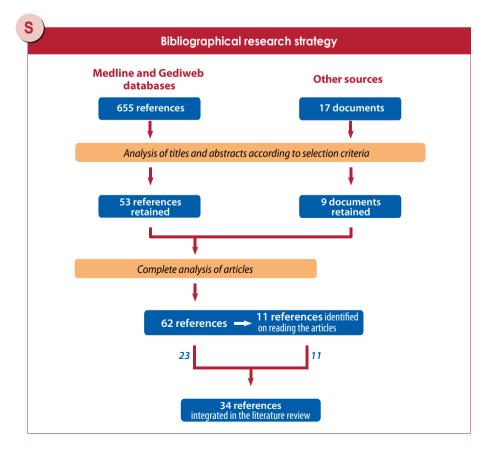
The WHO definition allows several accepted definitions of polypharmacy (WHO, 2004). The first part of the definition refers to the concurrent administration of medications and the word 'many' does not prejudge the excessive nature of this number. The terms "at the same time" provide a first indication regarding the temporal conditions under which polypharmacy is measured: medications that are administered simultaneously.

The second part of the definition on the contrary indicates excess medication and implicitly introduces the notion of drug misuse. In this case, polypharmacy refers to the administration of more drugs than clinically necessary (Hanlon *et al.*, 2001). By extension, polypharmacy is said to be 'appropriate' when the prescription of numerous medications is justified, and "inappropriate" when wrongly or indiscriminately prescribed (Aronson, 2004; Duerden *et al.*, 2013).

The time slots used to measure polypharmacy allow several types to be distinguished. Simultaneous polypharmacy corresponds to the number of drugs concurrently taken by a patient on a given day (Fincke et al., 2005; Kennerfalk et al., 2002). This indicator allows the study of complex dosing regimens, the risk of drug interactions, the occurrence of multimedication episodes, their frequency and duration, and to identify transitory factors that can increase the number of medications administered at a given time, such as hospitalisation or acute illnesses (Bjerrum et al., 1997; Fincke et al., 2005; Slabaugh et al., 2010). It can be estimated by counting the number of drugs taken on a random day or the average taken on several consecutive days or at regular intervals. It is sometimes expressed in terms of annual prevalence, defined as the number of persons having had at least one episode of polypharmacy, or in terms of monthly incidence (Slabaugh et al., 2010; Bjerrum et al., 1997). When the final value of the indicator results in the calculation of an average, this method will take into account the treatment of chronic diseases with greater precision and will moderate the number of medications used for acute illnesses and medications taken periodically or non-continuously (Kennerfalk et al., 2002). A variant of this definition imposes that the simultaneous use of numerous medications should be prolonged through time; at least 60 consecutive days quarterly, for example (Veehof et al., 1999, 2000).

Cumulative polypharmacy, also known as multiple medication (Hovstadius et al.,2010a), is defined by the sum of different medications administered over a given period of time (Fincke et al., 2005). Numerous studies use a three month period, the time necessary to take into account 95% of prescriptions based on the standard prescription renewal time (three months) [Bjerrum et al., 1997; Haider et al., 2009; Hovstadius et al., 2009, 2010a]. Other periods (six months, twelve months) have also been used. The longer the period of observation, the higher the prevalence of polypharmacy (Hovstadius et al., 2009; Bjerrum et al., 1998). This indicator is estimated by cumulating all the medications administered over the period taken into consideration, whatever the date and duration of the treatment. It is interesting in that each new medication carries its own risk of adverse effects. It gives equal weight to medications prescribed for a short period which is added to the total whatever the duration of its use. It also allows studying the cost of prescriptions as it includes all medications.

Continuous polypharmacy is the third type of indicator which is similar to cumulative polypharmacy but limited to medications taken for prolonged and regular periods. It only takes into account medications present in two given time periods spaced by an interval of six months, for example (Fincke *et al.*, 2005), or by tak-



ing into account only medications present in the preceding quarter (HQ&SC, 2011) and the following quarter (Grimmsmann et Himmel 2009). It thus answers the following question: 'How many drugs are administered continuously?' It completes the cumulative polypharmacy indicator by difference in that it shows how shortterm treatments are added to continuous in-depth treatments (Fincke et al., 2005). A variant of this indicator identifies medications for which prescription has been repeatedly renewed over the course of the year, usually with a frequency of three renewals per year (Carey et al., 2008; Cahir et al., 2010).

Some authors consider that, from the theoretical point of view, only the concept of simultaneous polypharmacy should be taken into consideration as it is this concurrent administration of numerous drugs that carries the greatest health risk for patients. They nevertheless recognize that the measurement of cumulative polypharmacy is easier to carry out and can be used effectively (Bjerrum *et al.*, 1997; Hovstadius *et al.*, 2010a).

Finally, the literature abounds with more complex definitions. Certain authors replace the number of medications administered by notions such as the existence of drug interactions, inappropriate prescribing in relation to diagnosis, prescription of contraindicated medications and inappropriate dosages or treatment durations (Bushardt et al., 2008). The notion of polypharmacy is often confused with inappropriate prescribing (Maggiore et al., 2010). Other than the fact that these definitions move away from the original meaning of "multiple" or "numerous"medications, and ignore the risks specifically related to multiple drug taking (poor observance, pharmacodynamic problems), their use requires data, and more especially clinical data, that is often inaccessible on a large scale.

Which medications should be included in the measurements? What data?

A drug is most frequently identified by the fifth class of the WHO ATC classification (Anatomical Therapeutic Chemical Classification System) which corresponds to the drug's active ingredient (Bjerrum *et al.*, 1998; Hovstadius *et al.*, 2009). Certain

medications are occasionally excluded from the measurement: topical agents and local action drugs, vitamins, minerals, herbal medicines, vaccines, homeopathy or drugs classified as "diverse" in the ATC classification (contrast agents, diagnostic tests, etc.) [Jyrkka *et al.*, 2009b; Haider *et al.*, 2009; Steinman *et al.*, 2006].

Data collection methods are varied: medical files, pharmaceutical registers, reimbursement data, and patient interviews. The data collection method strongly determines the information that will be available: prescription or over the counter, posology and duration, delivery, reimbursement. More often than not, only prescription drugs or reimbursed drugs are taken into account which under-estimates pharmaceutical consumption and the risks of drug interaction (Gnjidic *et al.*, 2012; Maggiore *et al.*, 2010).

Data collection methods also determine the feasibility of calculations. The measurement of simultaneous polypharmacy therefore requires information concerning the duration of administration for each drug. To counter the absence of this information, certain authors recommend using the Defined Daily Dose⁵ (DDD), whilst indicating one of its major limitations, the gap between DDD and national prescribing practices (Bjerrum *et al.*, 1997).

No consensus on the medication threshold defining polypharmacy

Numerous thresholds have been identified in the literature regarding the number of medications above which polypharmacy is considered to exist (Fulton et Allen, 2005; Hajjar et al., 2007; Bushardt et al., 2008). Certain thresholds are used more frequently than others, essentially 5 medications or over (Jorgensen et al., 2001; Bjerrum et al., 1999, 1998; Grimmsmann and Himmel, 2009; Haider et al., 2009; Hovstadius et al., 2010; Linjakumpu et al., 2002; Viktil et al., 2007; Hovstadius et al., 2009, Kennerfalk et al., 2002) and 10 medications or over (Jorgensen et al., 2001; Haider et al., 2009; Jyrkka et al., 2009b, 2009a, Hovstadius et al., 2010a).

The 5 medication threshold derives its justification from the linear growth of adverse effects the higher the number of medications. Certain authors even propose a more detailed segmentation of the threshold by using "5 to 7" and "8 and over" to take the increased risk into account (Preskorn et al., 2005). Other thresholds are also used. Steinman et al. (2006) for example propose a threshold of 8 medications justified by the fact that below this number, the risk of under-use is greater than the risk of polypharmacy or inappropriate prescription. Other authors use the threshold of 6 medications or over without any specific justification (Bushardt et al., 2008). One study suggests using ROC curves (Receiver operating characteristics) of sensitivity and specificity so as to evaluate the threshold beyond which polypharmacy carries a serious health risk (Gnjidic et al., 2012).

Certain authors define polypharmacy according to the number of medications administered. They thus consider the administration of 2 to 4 medications as "minor polypharmacy" and the use of 5 medications and over as "major polypharmacy" (Bjerrum et al., 1997; Bjerrum et al., 1998, 1999; Veehof et al., 1999). More recently, the term 'hyperpolypharmacy' (Gnjidic et al., 2013) or 'excessive multi-medication' (Haider et al., 2009; Jyrkka et al., 2006; Hovstadius et al., 2010a) have appeared to designate the consumption of 10 or more medications. In an article published in 2014, the consumption of over 10 medications is now considered as major whereas 20 medications or over is considered excessive (Kim et al., 2014). In parallel, the consumption of 5 medications or under is now considered as "non-polypharmacy" (Jyrkka et al., 2011) or "oligopharmacy" (O'Mahony et O'Connor, 2011).

The prevalence and signification of polypharmacy varies according to the indicator used

The indicators tested

From this review of the literature, we retained 4 polypharmacy indicators. Three indicators represent simultaneous

⁵ The Defined Daily Dose (DDD) is a comparison unit proposed and recommanded by the World Health Organisation (WHO), which represents the theorical dose for an adult of 70kg in the main indicators of the product.

| Tested indicators measuring polypharmacy | | | | |
|---|--------------|---|--|--|
| | | Indicator name | Calculation | Sources |
| | simultaneous | One day at random | Total current prescriptions, one day taken at random during the year of the study | Kennerfalk, Ruigomez <i>et al.,</i> 2002 |
| | | An average day, year | Total current prescriptions per day, annual average | Bjerrum, Rosholm <i>et al.,</i> 1997 |
| Polypharmacy | | An average day, 20 days | Total current prescriptions per day, average over 20 days eah with a 2 week interval | Fincke, Snyder et al., 2005 |
| Polypha | cumulative | Quarterly | Total number of mediations prescribed over the quarter, average over four quarters | AOK (Kaufmann-Kolle et al., 2009) ; Bjerrum, Rosholm et al., 1997 |
| • | continuous | Prescribed at least 3 times during the year | Total number of medications prescribed at least three times during the year | PAERPA programme indicator*; Carey, De Wilde <i>et al.</i> , 2008; Cahir, Fahey <i>et al.</i> , 2010 |
| * Definition of polypharmacy used in the PAERPA programme: www.has-sante.fr/portail/upload/docs/application/pdf/2014-09/cadre_referentiel_etp_paerpapolypathologie.pdf | | | | |

polypharmacy and one, cumulative polypharmacy. To these we added a continuous polypharmacy indicator, also found in the literature and retained within the PAERPA program framework (Table).

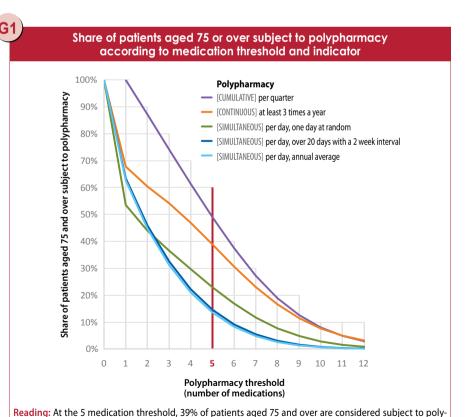
The IMS Health Disease Analyzer prescription database

These indicators were tested in the IMS Health Disease Analyzer (DA) database. DA collects data from a panel of voluntary French general practitioners and allows monitoring their patient's consultations and prescriptions. The scope retained here concerns patients aged 75 and over having had at least one drug prescription between April 1st 2012 and March 31st 2013. This choice was supported by the literature which shows that polypharmacy essentially concerns elderly patients, and it also corresponds to the population targeted by the PAERPA program. GPs having received less than 20 patients during the period under consideration were excluded. Our analysis was thus based on 69,324 patients and 687 GPs. These physicians transmit information on all consultations or visits for which medical files are computerized. In practice, the majority of data collected concern consultations in the GPs surgery which, given the frequency of these visits among the elderly in this age group (40% of sessions), leads to an under-estimation of the prevalence of polypharmacy from this data source.

Medications are identified by level 5 of the WHO ATC classification; that is to say from the active ingredient. Fixed dose combinations count for as many medications as the number of active ingredients they contain. Information on dosage and prescription duration allow the precise calculation of simultaneous prescription indicators. Local action agents, herbal medicine and homeopathy were excluded.

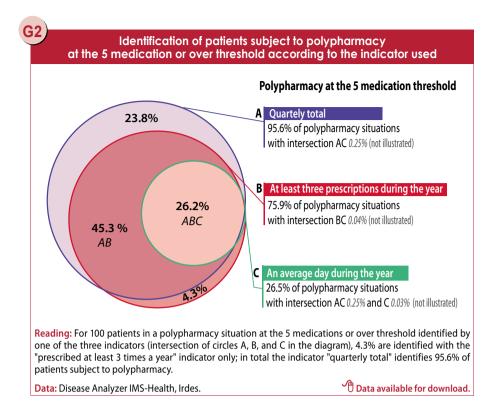
Results

The prevalence of polypharmacy varies according to the indicator used (Graph 1). Observed prevalence is higher using cumulative and continuous polypharmacy indicators than with simultaneous polypharmacy indicators. More than prevalence, which is dependent on the data and medications included in the calculation, it is interesting to observe the difference in prevalence that can double or triple according to the indicator used. The simultaneous polypharmacy indicators give the lowest rates. At the 5 medications threshold, polypharmacy thus concerns 14% of patients aged 75 and over using the simultaneous polypharmacy indicator "on an average day" and "20 days with an interval of 2 weeks" and 23% with the simultaneous polypharmacy indicator "one day taken at random". The highest rates are obtained with the cumulative polypharmacy indicator "quarterly" with 49%, and intermediate rates of 39% with



Data: Disease Analyzer IMS-Health, Irdes.

Data available for download.



the continuous polypharmacy indicator "prescribed at least 3 times during the year".

Among the simultaneous prescription indicators, "one day taken at random" captures short-term treatments cumulated with permanent long-term treatments. These short-term treatments are smoothed out by the indicators "annual average" or "average over 20 days". For the cumulative or continuous indicators, the "quarterly" indicator includes all prescriptions whether related to acute or chronic illnesses whereas the indicator "prescribed at least 3 times during the year" privileges treatments for chronic illnesses or repeated treatments.

Discussion

The observation of differences in prevalence according to the indicator used are numerous in the literature. Following the definition used (simultaneous, cumulative or continuous polypharmacy) the percentage of patients using 10 medications or over varies for example from 2% to 6% in the population of American veterans (Fincke *et al.*, 2005). Bjerrum *et al.* (1997) estimate that 80% of individuals identified as subject to major polypharmacy using the indicator for the maximum number of medications concurrent-

ly administered on a given day gave the same result with the three month cumulative indicator, but showed that only 69% were subject to major polypharmacy using the "average number of medications used daily" indicator.

The prevalence rates obtained follow an ascending order between simultaneous polypharmacy indicators and the "quarterly" cumulative indicator. The simultaneous prescription indicators "per day, average per year" and "per day, average over 20 days" give the lowest results as the value of the indicator results from the calculation of an average which limits the short-term treatments included. The cumulative prescription indicator on the contrary gives the highest results as all prescribed medications over the quarter are taken into account, whatever the treatment duration.

The estimations of prevalence rates for polypharmacy conducted here are very low compared to other French studies. Very recently, Beuscart *et al.* (2014) using Health Insurance data in the Nord–Pasde-Calais region, estimated that 35% of persons aged 75 and over had been administered over 10 medications over the three month period of the study, with a median of 8.3 medications. Our average of 3.7 medications prescribed 3 times

a year is also very far removed from the 7 medications prescribed 3 times per year, a result advanced within the framework of preliminary discussions on the PAERPA indicators⁶.

The reasons for these difference are related to the characteristics of the database used. In effect, Disease Analyzer only provides information on the panel GPs prescriptions but not prescriptions from other GPs or health professionals consulted. In addition, only consultations that took place in the GPs surgery are registered, hospital or home visit prescription data are not collected. The under-estimation of prescriptions related to visits can be explained in two ways: on the one hand, persons in this age group that consult the GP in his surgery are certainly in better health and therefore have less drug prescriptions than those visited in their homes and on the other, for a years observation for a given person, only prescriptions delivered during consultations are registered in the database, which under-estimates the number of medications prescribed to these individuals.

These limitations do not, however, call into question the observed differences in prevalence according to type of indicator, differences observed within a single database.

* * *

The indicator retained will depend on what is to be observed or measured. There are several ways in which polypharmacy indicators can be used. In a first case, it is the health risks carried by excessive medication, and the attempt to reduce adverse effects. In this situation, it is preferable to propose cumulative type indicators (the quarterly indicator in our example) that takes into account each medication added to the list and likely to generate adverse effects. These indicators are also the best adapted for the analysis of inappropriate prescriptions which requires data on all medications administered as illustrated by the works of Beuscart et al. (2014) on the prescription of anticholinergics. If the aim is more specifically to study drug interactions at individual level, it is more

http://www.igas.gouv.fr/IMG/pdf/rapport_ comite_national_pilotage_--projets_pilotes.pdf, consulted on November 17th 2014.

appropriate to use simultaneous polypharmacy indicators in order to appreciate risk exposure on a daily basis from the combination of administered medications as well as variations in the number of medications administered over short periods. However, these simultaneous prescription indicators which require information on dosage and treatment duration are often difficult to obtain and greatly undermine episodes of acute illness even though these episodes by their non-routine nature, can be a source of error on the part of doctors or patients.

In the second case, it will be the study of the therapeutic and also financial burdens of chronic disease on an individual. Intercurrent illnesses and short-term treatments are no longer taken into account and only medications administered continuously will be considered important. The continuous polypharmacy indicators are the most useful in this situation. This type of indicator also makes it possible to question the main treatment that is indispensable given the patient's comorbity and to define the necessary polypharmacy.

As a result these indicators are highly complementary and used together, provide a broader overview of the use of medication. However, it should not be forgotten that if polypharmacy is generally related to inappropriate prescribing, it is not sufficient on its own to identify them. Counting the number of medications does not allow distinguishing between those that are justified for a given pathology and those that are not. The analysis of drug prescriptions among the elderly therefore requires

completing information on polypharmacy with target indicators of inappropriate prescribing according to the research objectives or the evaluation intended. If the aim is, for example, to reduce hospitalizations among the elderly, the inappropriate prescription indicators will attempt to identify the administered medications that increase the risk of falls, for example, such as long-acting benzodiazepines, diuretics or anticholinergics.

The review of the literature presented in this article constitutes a first phase of research into polypharmacy. It will be continued with a more in-depth analysis of the mechanisms leading to polypharmacy by examining prescriber and patient characteristics and also the care pathways of elderly persons.

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