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PRESCRIBING CASCADE. A PROPOSED NEW WAY TO EVALUATE IT

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Abstract Prescribing cascade is defined as the situation in which a first drug administered to a patient causes adverse event signs and symptoms, that are misinterpreted as a new condition, resulting in a new medication being prescribed. The cascade may have multiple steps and differ in complexity and severity. Despite being well identified, prescribing cascade is an increasingly common problem in medical practice. It constitutes a warning about irrational use of medicines that puts health at risk and increases treatment costs if it is not taken into account. In this article, representative cases taken from Hospital General de Agudos Dr. Cosme Argerich pharmacovigilance database were selected to assess a proper score and an algorithm that define the probable prescribing cascade.

Key words: prescribing cascade, adverse drug reaction, polypharmacy, pharmacovigilance

Resumen ***Prescripción en cascada. Una nueva propuesta para evaluarla.*** La prescripción en cascada identifica la situación generada tras la administración a un paciente de un medicamento que le provoca un evento adverso, el cual al no ser debidamente reconocido como tal por el profesional desencadena nuevas prescripciones farmacológicas que pueden agravar o generar nuevos eventos adversos. Por ello, de acuerdo a la idiosincrasia de cada paciente, la cascada puede tener múltiples pasos y diferir en complejidad y gravedad. A pesar de estar identificada, la prescripción en cascada es un problema cada vez más común en la práctica médica y una advertencia sobre el uso irracional de los medicamentos que pone en riesgo la salud e incrementa sus costos si no se tiene en cuenta. En este artículo, se seleccionaron casos representativos tomados de la base de datos de farmacovigilancia del Hospital General de Agudos Dr. Cosme Argerich para probar un nuevo *score* y un algoritmo de decisión, que evalúen la supuesta cascada prescriptiva.

Palabras clave: prescripción en cascada, eventos adversos medicamentosos, polifarmacia, farmacovigilancia

Prescribing cascade (PC) by definition indicates the use of additional drugs to treat an iatrogenic-induced condition by a first drug (adverse drug reaction or ADR) in the wrong idea that this is a different medical event (but not the ADR) requiring obligatory treatment, and whose outstanding feature is that it could have been prevented if first drug had been properly used or the ADR recognized.

PC is a relatively new term; introduced by Rochon & Gurwitz in 1995 to identify a major geriatric problem[1], nowadays it is an example of the new challenges to medicine[2] despite its little worldwide impact as evidenced by the unique 27 clear citations about PC found in PubMed to date.

Due to the availability of more and better treatments, PC might signify a major pharmacovigilance (PVG) problem for the next years and, if it does not take it into account or the medical staff is not properly trained in PVG, it could trigger an exponential increase of the health care costs[3, 4].

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Since adverse effects and poorly understood drug-drug interactions represent a huge economic, ethical and legal burden for the worldwide communities[1-4], our group has believed necessary to create tools to assess these kinds of problems and to provide digested data for a correct decision-making in PVG[5, 6].

Taking into account the above mentioned, the aims of this work were: To define a score to precise and evaluate PC and its severity, to define a useful algorithm for PC prevention, and to present some representative cases of drug-induced adverse events that afterwards required pharmacologic treatment to exemplify the PC evaluation.

Material and methods

Score and algorithm for evaluating PC: A new score for determining PC was elaborated and tested in a few representative cases. The score comprises four questions with two to four options and a range from 0 or minimum value to 8 or maximum value (see Fig. 1). It is assumed PC if obtained score is 4 or more (50% of the maximum score), taking this value as provisional cutoff value. The score was also thought to reflect the PC severity; so, the higher the score the greater its severity. A proper algorithm for prevention of a given PC was generated. It comprises five YES-NO decision questions (see

Fig. 2) to test certain particularities; for instance, knowledge about PC, facts of an established treatment or certain drug properties. In any case, if the obtained response is YES the preventability of a PC is defined.

Case selection and ethics: Cases were chosen from PVG database of the Hospital General de Agudos Cosme Argerich, a tertiary care Institution dependent of Buenos Aires city health network. The Institutional PVG Committee of the Hospital, on function since June 2008, is responsible for generating and maintaining the mentioned database. Multiple probable PC cases were detected and discussed by independent evaluators following the next three items:

- Existence of a trigger ADR whose causality has been established by the Naranjo Score, even though their final diagnosis were delayed or improperly performed. Naranjo Score is suggested by the World Health Organization to evaluate causality of ADRs[7].
- Existence of a second drug to treat the former reaction.
- Existence of a new adverse event, attributable or not to the second drug.

The most significant and illustrative cases were selected to show the score utility. The protocol and data handling procedures were authorized by the Institutional Review Board of the Hospital, following the ethical principles of Helsinki Declaration and the Argentinian rules for protection of individual data.

Existence of ADR, either expected or unknown:	
Doubtful	0
Yes	1
Yes, but misunderstood	2
Action followed against the ADR:	
Treatment discontinuation	0
Continued with dose reduction	1
Continued unchanged or with another drug of the same group	2
Existence of a second drug treatment for the ADR:	
No	0
Yes	1
Overall result of this new treatment:	
Patient improves	0
Patient worsens or remains unchanged	1
A new ADR appears	2
The new ADR requires a third drug treatment	3
Sum (minimum required is 4)	

ADR: Adverse drug reaction.

Fig. 1.– The proposed score for defining prescribing cascade (PC).

Results

Eight, both gender (4 male; 4 female), 18-67 year-old patients with several conditions were selected on the basis of their ADR type and PC probability, and included in this analysis. The **Annexed Note**, at the end of this article, shows a brief medical data and case description of the elected patients.

Table 1 summarizes the available data. As it can be seen, the antiemetic metoclopramide and the beta-lactam imipenem, two widely prescribed drugs in our country, were the predominant inducers of ADRs. All cases were probably-related (75%) or possibly-related ADR (25%); four ADRs induced were Central Nervous System (CNS) disor-

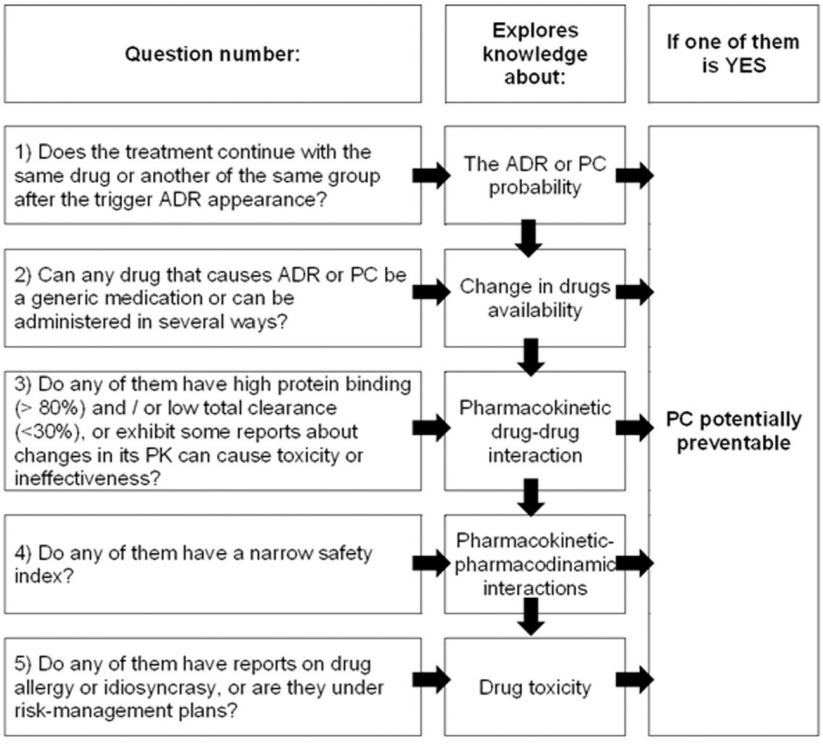

Fig. 2.– The proposed algorithm for prescribing cascade (PC) prevention.

TABLE 1.– *Summary of cases and results obtained after the application of prescribing cascade (PC) score and algorithm for prevention*

Case	Drug induces ADR	Naranjo Score*	Drug cascade	PC Score**	Algorithm-question
1	Metoclopramide	6	Trihexyphenidyl-lorazepam	8	YES Q1
2	Chemotherapy	4	Several antibiotics-NSAIDs	6	YES Q1
3	Metoclopramide	5	Lorazepam-antiepileptics	5	YES Q1
4	Imipenem	8	Meropenem-phenytoin	5	YES Q1
5	Imipenem	4	Valproic acid-levetiracetam	7	YES Q3
6	Amiodarone	6	Levothyroxine	4	NO
7	Metoclopramide	6	Loperamide	6	YES Q1
8	Lapatinib	6	Fibrates-metoclopramide	7	YES Q5

** Naranjo score options are: Defined: 9 or more. Probable: 5-8. Possible: 1-4. Doubtful: 0 or less.*
***PC is defined if the sum of score is 4 or more (the higher the score the greater severity of PC).*

ders and two metabolic. Interestingly, it should be noted that almost all of ADR inducers have been produced a poly-drug PC. When the new score was applied, all patients showed a value of 4 or more so it was concluded PC for all these cases. Also, with the proper algorithm, seven out of eight patients (87.5%) showed a PC that could be considered as preventable. Again, it should be noted more than a half of the cases could have been prevented if the situation had initially been recognized (situation that could be demonstrated by the number of YES response in question 1).

Finally, the published cases-report by Liu, et al.[8] and Nguyen & Spinelli[9] were reviewed under these PC score and algorithm and the obtained results were: 8 and preventable (by question 1) in both cases.

Discussion

PC is a recently coined term; it is cited more frequently into primary care or geriatric review articles[1-3, 10-12], albeit described in case-report papers[8, 9] and studied in retrospective cohort trials too[13-15]. The issue was posed in the United States and Canada with a few repercussions in European Union and Oceania, unlike the often related term Preventable ADR, which is already well established[16]. Therefore, it is not surprising that there are not up to date Latin-American or Argentinian publications about PC.

In this article we reviewed 8 cases. that we believed were the most representative to display PC. In them, no distinction was made between ages, since PC is a problem both in young and elder people. Compared this information with the few articles already published it can be seen they are not exactly the same compounds involved in PC except metoclopramide, but CNS ADRs appear to be a constant. This could be explained in part by the fact that proclorperazine and thiazide diuretics (prominent PC triggers in some of the cited papers) are not first choice drugs in our country.

Nevertheless, the primary care literature is now starting to uncover how certain treatments used to treat conditions not recognized as ADR often cause new ones, especially when they are applied without proper knowledge, and hence indicate strong recommendations about the topic[2, 10, 17]. On the need for better measuring the ADRs impact in daily medical practice, the use of scores or algorithms could detect potential signs of drug misuse[5, 6]. Thus, this work was performed to fulfill that.

Unfortunately, a weak aspect of this work is where or how to set the PC score cutoff value because there is no prior test to compare it. To define and compare that, subjective clinical risk estimation could be made following the specificity-sensibility format (low-high) and then, build a Receiver Operating Characteristic curve. This putative risk estimation should include some features of case data; for instance, number of drugs used, ADRs generated, or severity of the former disease. In this sense, low–high equate to 4-5 – 6-8 values of PC score. The few patients included in this work did not allow making any analysis, but preliminary estimates might predict that when a cutoff is low there would be an excess of false-positive values. Using a cutoff of 4 all cases, including troublesome or uncertain ones, arise as PC. However, if it would be used 5 (a more strict point to avoid any false-positive) the score sensitivity would be lower and might include false-negative cases.

It may be concluded that a treatment of ADR is often performed without a proper pharmacological knowledge[6, 18, 19]. Since futile polymedication enhance the chances of developing new diseases, the resulting polypharmacy represents a major health risk, raises senseless health costs, and generates potentially preventable morbidity and mortality. With this easy PC score and algorithm it is intended to define the problem and also to raise awareness among health professionals.

Conflict of interests: None to declare

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Annexed Note

Case 1: 18 year-old woman with non-responsive nausea by acute renal failure received metoclopramide in increasing doses. The patient developed sustained dystonia and because the symptoms were interpreted as a possible epileptic event, lorazepam was administered. This drug caused an excessive sedation, hindering the correct diagnosis. Multiple studies were performed and organic focus was dismissed. It was interpreted as an adverse reaction generated by metoclopramide overdose. Anticholinergic drug (trihexyphenidyl) was administered with reversal of the symptoms. ADR retrospective diagnosis: Metoclopramide induced dystonia and lorazepam induced sedation.

Case 2: 21 year-old man with febrile neutropenia following chemotherapy of acute myeloid leukemia received a broad-spectrum beta-lactam. Thereafter, the patient began with chills and high fever (40 °C). For this reason, despite retrieving the count of white blood cells, NSAIDs and drugs against Gram positive, viral and fungal germs were added. Because of multiple negative cultures and other tests, medication was suspended; simultaneously, chills and fever ameliorated and after imipenem discontinuation, completely disappears. ADR retrospective diagnosis: antibiotic-induced fever.

Case 3: 45 year-old male patient under epilepsy treatment and no seizures in the last three years, received high doses of metoclopramide for nausea. Shortly after, he developed a generalized tonic-clonic seizure episode. During hospitalization antiepileptic drug was changed, multiple studies showed no electrolyte disorders and no CNS organic damage were found. ADR retrospective diagnosis: decreased seizure threshold by metoclopramide D2 antagonism.

Case 4: 63 year-old male patient with no relevant history was hospitalized for abdominal symptoms. He received imipenem preventively. At the second day, he showed a generalized tonic-clonic seizure, so lorazepam and then phenytoin were administered. Electrolytes, CNS disorders and other causes were dismissed. The event was interpreted as drug-induced seizure. Meropenem therapy was initiated instead of imipenem but he repeated the seizure. The antibiotic was suspended and no more events occurred. ADR retrospective diagnosis: carbapenem-induced seizures due to anti-GABAergic effect.

Case 5: 20 year-old female patient with history of mental retardation and seizures was admitted for urinary tract infection and overall deterioration. According antibiogram, imipenem was started. After that, the patient presented an exacerbation her CNS symptoms; so she began to be treated with valproic acid. Several analyses ruled out pathologies justifying worsening of epilepsia. Meanwhile, she developed valproic acid-induced hyperamonemia. Valproic acid was suspended and levetiracetam was started. Retrospective diagnosis: decreased seizure threshold by imipenm anti-GABAergic effect.

Case 6: 67 year-old male patient with atrial fibrillation. He chronically received amiodarone. He developed hypothyroidism requiring treatment with levothyroxine. After that, the hypothyroidism symptoms reverted. ADR retrospective diagnosis: amiodarone-induced hypothyroidism.

Case 7: 36 year-old woman with history of eosinophilic gastroenteritis. She presented with epigastric pain and nausea. Treatment with metoclopramide was initiated. The following day she began with diarrhea. The symptoms are interpreted as part of her eosinophilic gastroenteritis and treatment with loperamide was started. Because the rest of the symptoms were improving, metoclopramide was suspended with reversion of diarrhea. ADR retrospective diagnosis: metoclopramide-induced diarrhea.

Case 8: 65 year-old woman with breast cancer. Under lapatinib she developed hypertriglyceridemia (up to 1400 mg%), so received a fibrate treatment. The last caused nausea and vomit and then she was medicated with metoclopramide. Finally, because of lapatinib intolerance the first treatment was suspended. Afterwards, the hypertriglyceridemia was decreased and fibrate-metoclopramide treatment was stopped. ADR retrospective diagnosis: lapatinib-induced dyslipidemia and fibrate-gastrointestinal symptoms.