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Prescribing cascades and medications most frequently involved in pain therapy: a review

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Abstract. – OBJECTIVE: The aging of the population and chronic pain represents topical issues in developed countries. These often translate into polypharmacy, inappropriate medications, and adverse drug events, with the risk of misinterpreting these latter with new medical conditions, generating what is referred to prescribing cascade. Prescribing cascades may lead to the prescription of new drugs, which could cause new potential side effects and unnecessary costs for individuals and healthcare systems. Therefore, the purpose of our review was to collect a good deal of prescribing cascades examples involving pain therapy medicines, to help clinicians minimize drug-related clinical outcomes.

MATERIALS AND METHODS: We search in MEDLINE database through PubMed, including 31 studies and 80 different examples of prescribing cascades.

RESULTS: The medications most commonly resulting in the initial drug therapy prescribed were represented by psychoanaleptics (27/80, 33.7%). Among adverse drug events, the most common one, misinterpreted as a new medical condition, was represented by tremor and extrapyramidal symptoms (20/80, 25%). As regards the new drug therapies prescribed for adverse drug events, the therapeutic subgroups most commonly resulting in the new drug therapy prescribed were represented by psycholeptics (12/80, 15%), and by anti-Parkinson drugs (12/80, 15%).

CONCLUSIONS: This study provides a list of several examples of prescribing cascades in pain medicine and is essential to raise awareness of the potential dangers they could involve in all patient populations. Collaboration between clinicians and clinical pharmacologists may lead to more appropriate polypharmacy schemes.

Key Words:
Pain medicine, Prescribing cascade, Polypharmacy, Inappropriate prescription, Older adults.

Introduction

The aging of the population represents a topical issue in developed countries. When we consider, for instance, the Aging Index for Italy in 2020, as the number of older adults per 100 people younger than fifteen years old[1], it is 178.4, equivalent to say 178.4 older adults per 100 young people under fifteen years old[2]. Aging population is not exempt from social, economic, and health problems that intersect and are associated with a significant increase in this population group's chronic diseases. This often translates in the use of polypharmacy, as described by the last National Report on Medicines use in Italy (OsMed Report 2019)[3], in which patients over 65 years old have a mean intake of 7.7 different drugs daily, with a maximum of 8.8 medications for those over the age of 85. It is widely known that polypharmacy is associated with an increased risk for adverse drug events[4-6], especially in older adults. We should also consider that potentially inappropriate medications use prevalence has remained high in the last decade[7-9], particularly since the continuous use of these potentially inappropriate prescriptions and the lack of safer pharmacological alternatives or non-pharmacological approaches represent a barrier to changing standard prescribing practices[10]. Among the various pathologies that most affect older adults, chronic pain is one of the most common medical conditions in developed countries. In Europe, about 19% of the adult population deals with moderate to severe chronic pain, with Italy being at third place in chronic pain prevalence[11]. This figure rises to an estimation of about 70% in cancer patients, especially in terminal stages of the disease, and in earlier phases in specific cancer types, includ-

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ing pancreatic and head and neck cancers[12]. Besides, increased survival represents an essential feature with the potential to experience chronic persistent pain, resulting from cancer treatments and the disease itself [13]. In Italy, there was a light, but constant increase in the prescription of pain medications in the last five years, with a total 2019 expenditure of 399.3 million of euro[3]. In this setting, multiple pain management and treatment guidelines have been produced. Still, rarely they offer an integrated approach that takes account of multimorbidity and polypharmacy in the real-world chronic pain patients. There are a variety of pharmacological options for the treatment of chronic pain conditions: opioids, nonsteroidal anti-inflammatory drugs, corticosteroids, as well as some medications used for neuropathic pain, as anticonvulsants, antidepressants, antipsychotics and benzodiazepines, and medicines for preventing some known adverse events, like proton pump inhibitors, antiemetics agents and laxatives. Concomitant use of these drugs, nevertheless, is accompanied by significant risks, especially the harmful consequences of sedatives, such as benzodiazepines[14], and opioids, which have been widely described in what is known as "the opioid crisis", because of the burden of drug misuse and abuse[14-16]. In this scenario of multimorbidity and polypharmacy, prescribing cascades might play an interesting role. This epithet was coined for the first time in the middle of the nineties, and described by Rochon et al on The Lancet[17], and The British Medical Journal[18]. A prescribing cascade has been described as the misinterpretation of an adverse drug event as a new medical situation, which may lead to the prescription of new drugs that could cause new potential side effects[17]. Consequently, these conditions are of extreme importance for public health because they could lead to adverse outcomes and unnecessary costs for individuals and for healthcare systems. Since some prescribing cascades are relatively easy to unearth[19], others are more difficult to recognize, especially in older adults, polypharmacy, and multiple pathological conditions. Besides, the medical literature regarding prescribing cascades and involved medications is often weak and limited to case reports. Therefore, the purpose of our review was to collect in the best possible way, from the published literature, a good deal of prescribing cascades examples, involving drugs most commonly used in pain therapy, to help clinicians and minimize drug-related clinical outcomes.

Materials and Methods

Search Strategy

This is a literature review; the search strategy aimed to find only published studies, with a two-step approach. Firstly, we search in the MEDLINE database through PubMed, from inception to August 15, 2020, using the following strategy: prescri* AND cascade*. Secondly, hand searches of the reference lists of all included articles were performed for additional studies of interest.

Types of Studies Included and Population

This review has considered for inclusion all study designs, without limitations, including therefore reviews, experimental and observational studies, case series, and case reports. We reviewed only articles in English or Italian. There were no other limitations on setting and population, including community-based, hospital-based, or residential care-based studies.

Methods of Review

For the first step of our research, identified resources were screened with the support of the software Abstrackr[20], exporting the list of searches directly from the PubMed search results, by PMID List, and uploading it into the software. One reviewer (P.NU.) excluded abstracts, if the notion of the prescribing cascade was not cited in the title and text. In contrast, another reviewer (G.C.) evaluated the full text obtained to find out examples of prescribing cascades involving pain therapy medicines. In the second step of our research, the same full-text reviewer (G.C.) hand-searched for reference lists of the included full-text articles. All the selections and inclusions were then discussed with two Pain Therapists (N.L., P.NO.), and discrepancies resolved. All examples of prescribing cascades were therefore summarized and organized in tables (Table I) (**Supplementary Table I**).

Results

Searches in the MEDLINE PubMed database yielded 468 unique articles, of which 48 were included in the full-text review process. Of these, 23 articles reported examples of prescribing cascades involving pain therapy medicines and were, therefore, included[18,21-42]. The hand-searches of reference lists of the included full-text articles led

Table I. The four most common examples of prescribing cascades, grouped by Adverse Drug Events (ADEs), misinterpreted as new medical conditions.

First drug prescribed	ADE	Second drug prescribed	Ref
Antipsychotics (including haloperidol, risperidone, levosulpiride) Antidepressants (including paroxetine, venlafaxine) Metoclopramide Valproic acid	Tremor/ Extrapyramidal symptoms	Beta blocking agents Primidone Gabapentin Anti-Parkinson drugs Diazepam	43, 21, 36, 45, 27
NSAIDs (including celecoxib) Trazodone Venlafaxine	Hypertension	Antihypertensives Prazosin Propranolol Lisinopril	21, 35
Quetiapine Venlafaxine	Arthritis	Meloxicam, Acetylsalicylic acid	21
NSAIDs Opioids (including tramadol) Antiepileptics Hypnotics and sedatives Haloperidol, risperidone	Dizziness	Prochlorperazine	33, 45, 23

Definitions and abbreviations: First drug prescribed, initial drug therapy of the prescribing cascade; ADE, adverse drug event, misinterpreted as a new medical condition; Second drug prescribed, medication prescribed for the treatment of adverse drug event; NSAIDs, Non-steroidal anti-inflammatory drugs; Ref, text references.

us to find other eight articles in which examples of prescribing cascades were described[43-50]. Of the 31 included studies, 12 were review studies[18,21,23,24,28,29,32,34,35,43,45,47], 9 were retrospective cohort studies[26,33,36,39,40,42,44,49,50], 5 were case reports[22,25,30,31,41], 2 were cross-sectional studies[37,38], and 3 were case-control studies[27,46,48]. Three studies were conducted between 1990 and 1999[18,46,48], seven between 2000 and 2009[24,32,37,40,44,49,50], and twenty-one between 2010 and 2019[21-23,25-31,33-36,38,39,41-43,45,47]. The included articles reported a total of 80 different examples of prescribing cascades (**Supplementary Table I**). For most of the examples, or to be precise for 48 of 80 examples (60%), the prescribing cascade consists of an initial medication, a subsequent adverse drug event, misinterpreted as a new medical condition, and a second medication prescribed. In 29 examples (36.2%), beyond the second medication prescribed, a second adverse drug event is also described, resulting from the use of the second drug. In one example a third drug for the treatment of the second adverse drug event is mentioned, while in two cases it is reported an additional third adverse drug event. **Supplementary Table I** lists all the examples of prescribing cascades reported in the studies included in this review.

According to the therapeutic subgroups of the Anatomical Therapeutic Chemical (ATC) Classification System, the medications most commonly resulting in the initial drug therapy prescribed were represented by psychoanaleptics (27/80, 33.7%), followed by nonsteroidal anti-inflammatory drugs (12/80, 15%). In terms of chemical substances, the drug most commonly reported as initial therapy was represented by venlafaxine (13/80, 16.2%), followed by celecoxib (6/80, 7.5%), and metoclopramide (6/80, 7.5%). The most common adverse drug event, misinterpreted as a new medical condition, was represented by tremor and extrapyramidal symptoms (20/80, 25%), followed by hypertension (10/80, 12.5%). As regards the new drug therapies prescribed for adverse drug event, the therapeutic subgroups most commonly involved were represented by psycholeptics (12/80, 15%) and anti-Parkinson drugs (12/80, 15%), followed by lipid modifying agents (8/80, 10%). In terms of chemical substances, the drug most commonly reported as new therapy was represented by prochlorperazine (7/80, 8.7%), followed by simvastatin (6/80, 7.5%), and meloxicam (6/80, 7.5%). Table I lists the four most common examples of prescribing cascades, grouped by adverse drug events, misinterpreted as new medical conditions.

Furthermore, depression (6/29, 20.7%) represented the most common adverse drug event, secondary to the medication for treating the first

adverse drug event of the cascade, followed by hemorrhage (3/29, 10.3%).

Discussion

This review study has as its purpose to collect a substantial group of prescribing cascades examples involving common drugs used in pain medicine, from the published literature, to help clinicians to find them out, and minimize drug-related clinical outcomes. Our research identified 31 resources in which examples of prescribing cascades were reported. As above-mentioned, these cascades include whole medication classes, as psychoanaleptics, anti-Parkinson drugs, and a variety of medications, particularly used in older adults. Among all the examples of cascades reported, an interesting one is represented by the use of proton pump inhibitors, which into daily clinical practice are often co-prescribed not only with nonsteroidal anti-inflammatory drugs, but also with the only corticosteroids or opioids. Inappropriate use of proton pump inhibitors, as widely documented in literature[51,52], especially in older adults, is a topic of great interest, both for clinical and economic implications. As well described by the 2019 American Geriatrics Society Beers Criteria®[53], and by the STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria[54], proton pump inhibitors may lead to an increased risk of Clostridium difficile infection, bone loss, and fractures. The same degree of interest could be directed to another medication class, like psychoanaleptics, which was the most common initial drug therapy prescribed in prescribing cascades examples we analyzed in this review. This therapeutic subgroup includes, among others, antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRI), or Serotonin-Norepinephrine Reuptake Inhibitors (SNRI), as well as anti-dementia drugs, used for Alzheimer's Disease[55]. The prevalence of depressive disorders in older adults, ranges from 1-5% in community populations to 42% in residents of long-term care structures, involving different variants and aspecific presentations[56]. In the older adult population, antidepressants appear to have similar effectiveness as in younger patients[57]. Still, elderly patients seem to be most disposed to develop adverse effects, such as hyponatremia, anticholinergic effects, and cardiovascular events[58]. For the reasons mentioned above, especially SSRI and venlafaxine, other than their extensive utilization, they may be involved in misinterpreting adverse drug events as new medical conditions. Moreover, we need to consider how older adults are often harassed by comorbidity and multimorbidity, and these conditions are accordingly attended by polypharmacy[59]. It is well known that polypharmacy is associated with an increased risk of adverse drug events, potentially inappropriate medications, drug-drug interactions, as well as higher costs for health care systems[60]. Over the last years, however, the concept of appropriate polypharmacy has become more and more discussed within the published literature[61]. If polypharmacy is often considered the assumption of five or more medicines in long-term use[61], Cadogan et al[62] define appropriate polypharmacy as the result of optimizing pharmacological treatments in multimorbid-affected patients. Within this approach, a recent commentary of McCarthy et al[63], highlights how prescribing cascades may also be recognized and intentional, and elaborates on the opportunity, for both recognized and unrecognized prescribing cascades, to differentiate detrimental or problematic prescribing cascades and appropriate ones. The prescribing cascade's appropriateness should be based on clinical considerations, along with the best available evidence, on the overall risk-benefit ratio and patient conditions and awareness. Since 2003 onwards, the notion of deprescribing has been delineated more closely[64-66]. The same deprescribing concept may be applied to detrimental prescribing cascades, as already reviewed by Brath et al[29], in order to improve medication safety and reduce inappropriate polypharmacy. Therefore, medication discontinuation has become a proactive process, being part of the continuity of patient care and pharmacological prescription[66-68]. Consequently, several deprescribing models have been designed in the fifteen years, including structured algorithms or practical guidelines[66,69-73], some of which providing a general description of the deprescribing process[66,70]. In contrast, others deal with specific medication classes[70,71], or population[72,73]. In this process, we should also consider different drug prescribing measures, including medication reconciliation, the reduction of potentially inappropriate medications, and drug-drug interactions. Besides, it is

crucial to have the best possible knowledge of prescribing cascades, especially for evaluating the overall risk of medication-induced harm in our patients.

Despite all the above-discussed qualitative measures of medication prescribing, we have to explain several limitations of the current article. First, this is a literature review, including only one (MEDLINE PubMed) database, among many. Second, language bias may have also been included as we collected only English and Italian resources. However, many studies were selected for inclusion, and no limitations on setting and population were applied. Yet, it must be added that the majority of the included resources detailed about older adults, even though prescribing cascades may also occur in younger patients. Another limitation of this study is that prescribing cascades have been reported in an orderly way, but we did not include possible interventions to reverse those detrimental situations.

Conclusions

This study provides a list of several examples of prescribing cascades involving pain therapy medications. As previously discussed, polypharmacy may be associated with inappropriate prescriptions, drug-drug interactions, and adverse drug events, like prescribing cascades, leading to clinical consequences and higher costs for health care systems. Furthermore, to the best of our knowledge, there are no prevalence studies[37,38] on the overall subject of prescribing cascades, except for individual medication classes. Consequently, further research is needed to understand all medications being involved in prescribing cascades, how to prevent them, and to reduce them in clinical practice. In this scenario, this study is essential to raise awareness of the potential dangers that prescribing cascades could involve, not only in older adults but in all patient populations, and, especially, in chronic pain patients. Collaboration between clinicians and clinical pharmacologists may lead to more appropriate polypharmacy schemes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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