appears at variable timepoints that depend on the half-life of each drug.[5,8,44-46]

Several studies conducted over the last decades have addressed increased suicidality (suicidal ideation, attempts, or behaviours) among antidepressant users. This severe adverse event might be attributed to the rebound effect,[8] assuming the half-lives of the drugs are taken into account when evaluating the phenomenon.[47-49] A meta-analysis[50] assessed the correlation between antidepressant use and suicidality in 4,582 paediatric patients and found an RR of 1.66 (95% CI, 1.02-2.68) in randomized trials of SSRIs for depression treatment and an RR of 1.95 (95% CI, 1.28–2.98) for all antidepressants across all indications.

Other meta-analyses found similar results in adolescents[51] and young adults,[52] and 1 case-control study[53] reported a significant risk of suicidality at the onset of treatment, after discontinuation, and during periods of dose changes, thus addressing the caution required when managing antidepressants.

Rebound effects of cholesterol-lowering drugs (statins)

In addition to reducing cholesterol biosynthesis, statins exhibit "pleiotropic" or "vasoprotective" effects that lead to improved endothelial function (increased nitric oxide bioavailability, inhibition of inflammation and thrombogenic responses, immunomodulatory actions, regulation of progenitor cells, and stabilization of atherosclerotic plaques). Along with a rebound increase in cholesterol production, experimental and clinical studies suggest that statin discontinuation induces a rebound deterioration of endothelial function (pro-oxidant, pro-inflammatory, and pro-thrombotic state), thus maximizing the vascular risk.[9,54]

Interventional[55,56] and observational[57-63] studies have shown that statin discontinuation (rebound effect) is associated with a significant increase in the risk of death (due to fatal vascular events), compared to maintenance and no treatment. A recent retrospective analysis[64] of data from 12,689 patients with ischaemic stroke showed that statin discontinuation at hospital admission was associated with a significantly higher risk of death (RR, 2.5; 95% CI, 2.1-2.9) compared to treatment maintenance.

Given the increasing evidence on the rebound effects of statins, both doctors and patients should be made aware of the risks inherent to discontinuation or withdrawal.

Rebound effects of gastric acid suppressants

All types of gastric acid suppressants (antacids, H_2 receptor inhibitors, and proton-pump inhibitors (PPIs)) induce rebound acid hypersecretion. Also, hypergastrinaemia has been found to occur as a secondary effect of long-term treatment. The rebound effect manifests at a given timepoint after discontinuation as a function of the half-life of each particular drug.[10,65,66]

Clinical evidence of rebound acid hypersecretion following PPI discontinuation was found in recent interventional studies,[67-70] in which it affected more than 30% of users.[71]

Because gastrin exerts trophic actions on several tissues, hypergastrinaemia might be associated with the development of advanced neoplasia in Barrett's oesophagus,[72] as well as of carcinoid tumours in Zollinger-Ellison syndrome and atrophic gastritis.[73] A cohort study[74] found a direct correlation between the increased incidence of gastric cancer and PPI use, thus suggesting that rebound hypergastrinaemia might represent a risk factor for the development of gastric cancer following excessive PPI use. Similarly, the increased incidence of gastric carcinoid tumours over the past 3 decades (400% among males and 900% among females) might also be associated with the indiscriminate use of PPIs.[75]

Although liberal PPI use is recommended in protocols for dyspepsia treatment,[76] health professionals ought to weigh their relative risks and benefits.

Rebound effects of antiresorptive drugs (bisphosphonates)

Bisphosphonates (BPs) promote increased bone mineral density (BMD) by inhibiting bone resorption through a reduction in osteoclast activity and thus represent the most widely used approach to reduce the risk of osteoporosis-related fractures. The biological effects (half-life) of BPs remain long after discontinuation as a function of their retention in the bone matrix. Although BPs do reduce the incidence of the "typical" fractures associated with osteoporosis, the occurrence of "atypical" subtrochanteric and diaphyseal femoral fractures has been recently reported in individuals who use BPs. A "rebound osteoclast activity" is believed to be the most likely systemic pathogenic mechanism underlying such fractures, as these occur independently from trauma and exhibit large radiological and clinical alterations, as well as significant morbidity.[12,77,78]

A case series[79] and observational studies[80-84] found an association between BP use over variable periods of time (3-60 months) and the occurrence of atypical fractures; a putative correlation with cumulative drug use was ruled out, as was the hypothesis that suggested hypermineralization (osteopetrosis) with microdamage accumulation as the pathogenic mechanism.[79,85] Additionally, experimental studies[77,86,87] indicate the occurrence of paradoxical osteoclast activity following BP discontinuation ("biphasic anti-osteoclastic action"), with rebound increases in markers of bone remodelling, eroded areas, and numbers of active osteoclasts. Also, other antiresorptive drugs (hormone treatments and monoclonal antibodies) were shown to induce similar effects.[77]

Although the incidence of typical hip fractures has decreased since the introduction of BPs, the incidence of atypical femur fractures has increased,[88] thus indicating the need for caution when managing such drugs.

Discussion

The rebound effect, a universal and automatic organic mechanism to maintain a constant internal environment or homeostasis, is liable to be elicited by all types of enantiopathic

drugs. As a function of the drugs' magnitude, such paradoxical reactions might induce severe and eventually fatal adverse events. Although the rebound effect only manifests in a very small fraction of individuals, it becomes an epidemiological concern when considering the exceedingly broad use of pharmacological treatments by the population.

The time interval between drug discontinuation and rebound effect appearance was similar among drugs with short half-lives, with an average of 10 days for ASA, 14 days for NSAIDs, 9 days for rofecoxib, 7 to 14 days for SSRIs, 7 days for statins, and 7 to 14 days for PIPs. The rebound effect lasted up to 30 days for rofecoxib, 21 days for SSRIs, and 30 days for PIPs. The length of treatment before discontinuation did not correlate with the risk of paradoxical events.

Similar to estimates for other drugs, LABAs cause 1 case of fatal rebound bronchospasm per 1,000 patient-years of use,[38] corresponding to 4,000-5,000 deaths in 2004 in the United States alone, and 40,000-50,000 deaths worldwide.[7] SSRIs cause 5 rebound suicidal manifestations per 1,000 patient-years of use among adolescents, corresponding to 16,500 cases of suicidal ideation or behaviours in 2007 in the United States alone.[8] BPs cause 1 to 3 episodes of paradoxical atypical fractures per 1,000 patient-years of use.[12]

The literature also addresses the risk of rebound effect inherent to the novel agents used in biological therapy,[89-91] as well as the excessive use of analgesics[92] and psychotropic drugs.[93,94]

Upon learning the preliminary results[95] of a study[23] that described the risks associated with ASA discontinuation, Richard S. Irwin, then president of the American College of Chest Physicians, observed that "this study does not only reinforce the importance of compliance with aspirin therapy in coronary patients, but it sends a message to all medical professionals that the decision to discontinue aspirin therapy should not be taken lightly". Similarly, McColl and Gillen[96] address the fact that the rebound induction of symptoms by PPIs "means that such liberal prescribing is likely to be creating the disease the drugs are designed to treat, causing patients with no previous need for such therapy to require intermittent or long-term treatment". Similar warnings have also been made regarding many of the above-mentioned drugs mentioned, thus indicating the relevance of the ability of the rebound effect to induce deep alterations to organic homeostasis.

Valuing the rebound phenomenon as a public health problem, recent studies have addressed the risks associated with the discontinuation of analgesics[97,98] and psychotropic drugs,[46,93,94] which are particularly relevant, given the widespread use of such pharmacological agents. Therefore, it is worth noting the probable occurrence of the immune reconstitution inflammatory syndrome (IRIS) following the discontinuation of natalizumab, a monoclonal antibody used as a biological therapy for multiple sclerosis, consequent to the rebound exacerbation of disease activity.[99-102] The advancement represented by biological therapy notwithstanding, discontinued use of immunomodulatory agents is also associated with a high frequency of paradoxical reactions in individuals receiving cancer treatment.[103,104]

For the notions described here – which, although orthodox, vigorously oppose the therapeutic model – to be widely assimilated, we suggest as a pedagogic proposal to include corresponding evidence when teaching physiology and pharmacology during courses for health professionals, as well as during discussions of clinical cases and the follow-up of patients who are assisted at hospitals, outpatient clinics, or at home.

Professionals at all levels of the healthcare system should be systematically aware of and properly oriented to the intrinsic dangers associated with the random and abrupt withdrawal of drugs so that they might duly advise their patients and establish programmes for drug tapering, while closely monitoring the subsequent effects.

Regarding scientific research, the studies described in the present review might be reproduced in our milieu and thus quantify the incidence of the rebound effect, the magnitude of its associated risks, and the effectiveness of preventive measures. Additionally, a multiplication of the number of reported examples will facilitate the admission of the existence of the rebound effect by health professionals.

Conclusion

A large number of severe and potentially fatal AE might be avoided if health professionals were oriented to recognize the occurrence of paradoxical reactions following the discontinuation of drugs that exert opposite actions to disease manifestations, thus minimizing the occurrence of rebound disease aggravation by reducing doses gradually and slowly or by restarting the drug. Although these are not traditionally considered adverse events, "drug discontinuation effects are part of the pharmacology of a drug",[15] and thus should be included when teaching modern pharmacology.

In a manner analogous to the homeopathic model of treatment that employs drugs that cause changes and symptoms similar to those exhibited by the ill individual (principle of therapeutic similitude) for more than 2 centuries, a novel therapeutic approach known as "paradoxical pharmacology" is emerging within modern conventional pharmacology. According to that approach, "exacerbating a disease might make use of the organism's compensatory and redundant mechanisms to achieve a beneficial long-term response"[105-109] (use of the bidirectional or biphasic effect).

Paradoxical pharmacology is conventionally associated with the use of beta-blockers (beta-adrenoceptor antagonists) and calcium channel blockers in congestive heart failure to improve ventricular contractility and reducing mortality[110,111]; beta-blockers for chronic asthma treatment to induce bronchodilation and reduce airway inflammation[112]; thiazides for diabetes insipidus treatment to reduce polyuria and increase urine osmolality due to their paradoxical antidiuretic effects[113]; arsenic trioxide (As_2O_3), a significant carcinogenic agent that has shown promise as a cancer treatment[114,115] (e.g., acute promyelocytic leukaemia); oral contraceptives to induce ovulation (and thus pregnancy) in women with functional sterility[116]; central nervous system stimulants (amphetamine, methylphenidate, and pemoline, among others) for hyperactivity, given the biphasic effects of these drugs,[117] among other examples. Notably, the doses required

to elicit the secondary and curative (paradoxical, rebound, or biphasic) effects of these drugs are much lower than those usually used to induce their primary effects (avoiding the worsening of the disease).

In an attempt to bridge the gap between disparate rationalities and to broaden the scope of the therapeutic by similars, during the last decade we developed systematics for the clinical applications of the rebound curative effects of 1,250 modern drugs.[118-122] According to this procedure, too ill individuals are prescribed drugs that cause adverse events similar to their disturbances (totality of symptoms) in an attempt to induce a paradoxical reaction of the organism against its exhibited disorders (http://www.newhomeopathicmedicines.com).

While keeping in mind the bioethical principles of "beneficence" and "non-maleficence", physicians should have the conviction and sufficient technical information to ensure that their actions will benefit patients and cause them the least possible harm, according to the Hippocratic aphorism *primum non nocere*. The present review aims to direct our professional colleagues' attention to the occurrence of the rebound effect, namely a severe, albeit unknown adverse event of modern therapeutics, for the sake of a safer and less iatrogenic clinical practice.

Conflicts of interest

The author declares no conflicts of interest.

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