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Rebound effects of modern drugs: serious adverse events unknown by health professionals☆

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A B S T R A C T

Objective: Supported in the Hippocratic aphorism *primum non nocere*, the bioethical principle of non-maleficence pray that the medical act cause the least damage or injury to the health of the patient, leaving it to the doctor to assess the risks of a particular therapy through knowledge of possible adverse events of drugs. Among these, the rebound effect represents a common side effect to numerous classes of modern drugs, may cause serious and fatal disorders in patients. This review aims to clarify the health professionals on clinical and epidemiological aspects of rebound phenomenon.

Methods: A qualitative, exploratory and bibliographic review was held in the PubMed database using the keywords 'rebound', 'withdrawal', 'paradoxical', 'acetylsalicylic acid', 'anti-inflammatory', 'bronchodilator', 'antidepressant', 'statin', 'proton pump inhibitor' and 'bisphosphonate'.

Results: The rebound effect occurs after discontinuation of numerous classes of drugs that act contrary to the disease disorders, exacerbating them at levels above those prior to treatment. Regardless of the disease, the drug and duration of treatment, the phenomenon manifests itself in a small proportion of susceptible individuals. However, it may cause serious and fatal adverse events should be considered a public health problem in view of the enormous consumption of drugs by population.

Conclusion: Bringing together a growing and unquestionable body of evidence, the physician needs to have knowledge of the consequences of the rebound effect and how to minimize it, increasing safety in the management of modern drugs. On the other hand, this rebound effect can be used in a curative way, broadening the spectrum of the modern therapeutics.

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Efeito rebote dos fármacos modernos: evento adverso grave desconhecido pelos profissionais da saúde

Palavras-chave:
Farmacologia
Efeitos fisiológicos de drogas
Efeito rebote
Efeitos adversos
Lei dos semelhantes
Homeopatia

RESUMO

Objetivo: Apoiado no aforismo hipocrático *primum non nocere,* o princípio bioético da não maleficência roga que o ato médico cause o menor dano ou agravo à saúde do paciente, incumbindo ao médico avaliar os riscos de determinada terapêutica por meio do conhecimento dos possíveis eventos adversos das drogas. Dentre esses, o efeito rebote representa um efeito colateral comum a inúmeras classes de fármacos modernos, podendo causar transtornos graves e fatais nos pacientes. Esta revisão tem o objetivo de esclarecer os profissionais da saúde sobre os aspectos clínicos e epidemiológicos do fenômeno rebote.
Métodos: Uma revisão qualitativa, exploratória e bibliográfica foi realizada na base de dados PubMed utilizando os unitermos 'rebound', 'withdrawal', 'paradoxical', 'acetylsalicylic acid', 'anti-inflammatory', 'bronchodilator', 'antidepressant', 'statin', 'proton pump inhibitor' and 'bisphosphonate'.
Resultados: O efeito rebote ocorre após a descontinuação de inúmeras classes de fármacos com ação contrária aos distúrbios da doença, exacerbando-os a níveis superiores aos anteriores do tratamento. Independente da doença, da droga e da duração do tratamento, o fenômeno se manifesta numa pequena proporção de indivíduos suscetíveis. No entanto, pode causar eventos adversos graves e fatais, devendo ser considerado um problema de saúde pública em vista do enorme consumo de fármacos pela população.
Conclusão: Reunindo um corpo de evidências crescente e inquestionável, o médico precisa ter conhecimento das consequências do efeito rebote e de como minimizá-lo, desse modo aumentando a segurança no manejo das drogas modernas. Por outro lado, este efeito rebote pode ser utilizado de forma curativa, ampliando o espectro da terapêutica moderna.

Introduction

According to Webster's New World Medical Dictionary,[1] "rebound" is defined as "the reversal of a response upon the withdrawal of a stimulus", while "rebound effect" is "the increased production of negative symptoms when the effect of a drug has passed or the patient no longer responds to the drug. If a drug produces a rebound effect, the condition it was used to treat may return even more strongly when the drug is discontinued or loses effectiveness". Also known as a "paradoxical reaction" of the organism, this phenomenon ironically makes individuals feel with greater intensity and/or frequency the same symptoms that were expected to disappear with the use of medications that exhibited actions opposite or contrary (enantiopathic) to the disease symptoms and physiological manifestations.

Adverse event (AE) or adverse reaction (AR) is defined by the World Health Organization[2] (WHO) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function". Although the rebound effect is a type of AE with potentially severe or even fatal consequences, this effect is scarcely disseminated and discussed among health professionals, who are thus deprived of crucial knowledge for safe modern drug management.

Overall, the rebound effect (paradoxical reaction) is the result of the organism's automatic attempts to return to its basal state (homeostasis) after having been altered by the primary effects of drugs. Because a characteristic of living beings is their ability to maintain a constant internal environment by self-adjusting physiological processes, homeostatic mechanisms are present at all levels of biological organisation, from simple cell mechanisms to the most complex mental functions.

The mechanism that underlies the occurrence of the rebound effect is not yet fully elucidated. According to the main hypothesis suggested to account for this effect, the cause might be an altered regulation and/or response capacity of the physiological receptors involved in the drug action mechanisms. Experimental evidence has shown that the rebound effect occurs at variable time intervals following the partial (e.g., dose change, receptor hypersensitivity, treatment initiation , tolerance etc.) or complete discontinuation of a drug, that the intensity of the ensuing symptoms is greater than that of the symptoms initially supressed by the drug, and that the duration of action varies.

We have conducted a systemic study on drug rebound effects during the last decades in order to establish the grounds of the principle of therapeutic similitude (homeopathy) vis-à-vis modern pharmacology.[3-12] This current updated review on the rebound effect aims to direct the attention of health professionals to the associated mechanisms, consequences, incidence, magnitude, and strategies to avoid

the occurrence of this poorly known adverse event that could result in severe consequences to the users of several classes of drugs, thus contributing to safer modern drug management.

Methods

To increase the body of evidence for and the understanding of the rebound effect vis-à-vis clinical and experimental pharmacology, an exploratory and qualitative literature review was performed in the PubMed database (2002-2012), using the keywords 'rebound', 'withdrawal', 'paradoxical', 'acetylsalicylic acid', 'anti-inflammatory', 'bronchodilator', 'antidepressant', 'statin', 'proton pump inhibitor', and 'bisphosphonate'. The articles were selected based on their titles and abstracts, and the full texts of those that addressed the investigated subject were analysed, as were studies cited by these articles that were not detected by the initial survey. The studies considered most relevant were included in the present review of the clinical and epidemiological features of the rebound effect.

Results

The rebound effect in modern pharmacology

Literature reviews[13-15] have described conceptual distinctions, evaluation criteria, and scientific evidence for the so-called "discontinuation or withdrawal syndromes" of various modern drugs (anticoagulants, anticonvulsants, antipsychotics, barbiturates, benzodiazepines, cimetidine, clonidine, corticosteroids, opiates, propranolol, and antidepressants, among others). This "rebound syndrome" is distinguished from the "reappearance of the underlying disease" that occurs in the absence of pharmacological drug actions, as rebound syndrome appears after (partial or complete) drug discontinuation and leads to symptoms and/or physiological manifestations more intense than those before treatment. Notably, the full manifestation of this phenomenon occurs after a given period of time that depends on the drugs' biological effects (*time-point*, or "half-life"). Therefore, gradual discontinuation of a drug is recommended to minimize this event.

The following examples illustrate the scope of the rebound effects associated with various classes of modern drugs.[3-12] Drugs for which the primary action promotes improvements in angina pectoris (beta-blockers, calcium channel blockers, and nitrates, among others) might increase the intensity and/or frequency of chest pain following their discontinuation. Antihypertensive drugs (alpha-2 adrenergic agonists, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, monoamine oxidase (MAO) inhibitors, nitrates, sodium nitroprusside, and hydralazine, among others) might lead to rebound hypertension following the end of their primary biological effects. Antiarrhythmic agents (adenosine, amiodarone, beta-blockers, calcium channel blockers, disopyramide, flecainide, lidocaine, mexiletine, moricizine, and procainamide, among others) might cause a rebound exacerbation of baseline ventricular arrhythmias. Antithrombotic drugs (argatroban, bezafibrate, heparin, salicylates, warfarin, and clopidogrel, among others) might promote thrombotic complications as a result of the rebound effect. Agents with primary vasoprotective effects (statins) might elicit rebound vascular dysfunction that favours the occurrence of paradoxical embolism.

Similarly, the discontinuation of psychiatric medication, including anxiolytics (barbiturates, benzodiazepines, and carbamates, among others), hypnosedatives (barbiturates, benzodiazepines, morphine, promethazine, and zopiclone, among others), central nervous system stimulants (amphetamines, caffeine, cocaine, mazindol, and methylphenidate, among others), antidepressants (tricyclic antidepressants, MAO inhibitors, and serotonin reuptake inhibitors, among others), and antipsychotics (clozapine, phenothiazines, haloperidol, and pimozide, among others), might trigger a rebound aggravation of the initial clinical condition. Anti-inflammatory agents (corticosteroids, ibuprofen, indomethacin, paracetamol, and salicylates, among others) might induce a rebound increase in inflammation, as well as rebound thrombosis (ibuprofen, indomethacin, diclofenac, salicylates, rofecoxib, and celecoxib, among others) due to their platelet antiaggregant actions. Analgesics (caffeine, calcium channel blockers, clonidine, ergotamine, methysergide, opiates, and salicylates, among others) might trigger rebound hyperalgesia. Diuretics (furosemide, torsemide, and triamterene, among others) might cause rebound sodium and potassium retention, with consequent increases in the baseline blood volume. Bronchodilators (adrenergic agents, disodium cromoglycate, epinephrine, ipratropium, nedocromil, salmeterol, and formoterol, among others) might induce rebound bronchoconstriction as a paradoxical reaction of the organism to treatment discontinuation. Antidyspeptic agents (antacids, H_2 receptor antagonists, misoprostol, sucralfate, and proton-pump inhibitors, among others) might increase hydrochloric acid and gastrin secretion as a rebound effect, thus aggravating the original clinical condition. Agents used to treat osteoporosis (bisphosphonates) might favour the occurrence of paradoxical atypical fractures due to a rebound increase in osteoclast activity.

Therefore, as demonstrated in clinical and experimental pharmacology,[3-12] the rebound effect exhibits some particular features: (i) it manifests in susceptible individuals; (ii) it is independent of the type of drug used or the individual's disease (symptoms); (iii) it appears following partial or complete drug discontinuation according to the individual's idiosyncrasy; (iv) it promotes a clinical state opposite to the drug's primary action; (v) the symptoms it induces are more intense than those before treatment; and (vi) the effect magnitude is proportional to the primary effect of the drug.

In addressing such phenomena, an increasing number of studies have indicated the occurrence of "severe" and "fatal" adverse events that are associated with the organism's paradoxical reaction.

Rebound effect of platelet antiaggregant drugs

Acetylsalicylic acid

Acetylsalicylic acid (ASA) is a non-steroidal anti-inflammatory drug (NSAID) that belongs to the non-selective cyclooxygenase

(COX) enzyme inhibitors; these enzymes catalyse the conversion of arachidonic acid into prostaglandins (COX-2) or thromboxanes (COX-1). ASA is widely used to prevent thromboembolism because it inhibits the actions of COX-2 and platelet aggregation. Clinical and experimental studies have reported the occurrence of rebound thromboembolism following the discontinuation of ASA and other platelet antiaggregant drugs, which has led to transient ischaemic attacks (TIA), acute myocardial infarction (AMI), and stroke in susceptible individuals.[5,6,16]

To assess the risks associated with ASA discontinuation, a meta-analysis[17] of 50,279 individuals at risk of coronary artery disease (CAD) compared "adherence to ASA therapy" in CAD prevention and myocardial revascularisation to "ASA discontinuation" in the incidence of acute CAD and in the implantation of drug-eluting stents. ASA non-adherence/withdrawal was associated with a 3-fold higher risk of major adverse cardiac events (*odds ratio* (OR) = 3.14; 95% confidence interval (95% CI) 1.75-5.61). Another meta-analysis[18] (49,590 individuals) showed that ASA withdrawal preceded up to 10.2% of acute cardiovascular syndromes, with intervals of 4 to 8 days in the case of acute coronary syndromes, 11 to 14 days in the case of acute cerebral events, and 18 to 26 days in the case of peripheral arterial syndromes.

Compared to treatment maintenance, observational studies found a 3 or 4-fold higher risk of severe vascular events (AMI, TIA, and stroke) following ASA withdrawal,[19-21] while 4% of such events occurred soon (6 to 30 days) after the discontinuation of platelet antiaggregant drugs.[22,23]

As rebound platelet aggregation was observed after the discontinuation of all classes of platelet antiaggregant drugs,[24-26] both physicians and patients ought to understand the appropriate management of such agents to reduce the risk of severe and fatal thromboembolic events.

Non-steroidal anti-inflammatory drugs

Similar to ASA, the occurrence of rebound cardiovascular events was also observed following the discontinuation of all types of NSAIDs (selective and non-selective COX inhibitors). Confirming the results of clinical and experimental studies that demonstrated the occurrence of rebound platelet aggregation after partial or complete NSAID discontinuation,[5,6,27,28] a systematic review[29] of 1.6 million individuals found a correlation between the occurrence of cardiovascular events and early NSAID treatment (< 30 days); compared to non-treatment, rofecoxib use at a doses of ≤ 25 mg/day and > 25 mg/day exhibited relative risks (RR) of 1.33 (95% CI, 1.00-1.79) and 2.19 (95% CI 1.64-2.91), respectively; while diclofenac, meloxicam, and indomethacin exhibited RR of 1.40 (95% CI, 1.16-1.70), 1.25 (95% CI, 1.00-1.55), and 1.30 (95% CI, 1.07-1.60). Another meta-analysis[30] of 145,373 individuals found a RR of 1.42 (95% CI, 1.13–1.78) for rofecoxib and 1.63 (95% CI, 1.12–2.37) for diclofenac.

A case-control study[31] that investigated the correlation between NSAID use and the risk of hospitalization for AMI found similar results for rofecoxib (RR, 1.36; 95% CI, 1.18-1.58), diclofenac (RR, 1.40; 95% CI 1.19-1.65), meloxicam (RR, 1.24; 95% CI, 1.06-1.45), and indomethacin (RR, 1.36; 95% CI, 1.15-1.61). Another case-control study[32] found a correlation between rofecoxib use and the first AMI event (RR, 1.67; 95% CI, 1.21-2.30). These events occurred at an average of 9 (range, 6-13) days after treatment initiation; additionally, the risk remained high during the first 7 days after rofecoxib discontinuation (RR, 1.23; 95% CI, 1.05-1.44) and returned to baseline levels between days 8 and 30 (RR, 0.82; 95% CI, 0.61-1.09), which is characteristic of the rebound effect. A retrospective cohort study (1999-2001) of 1.4 million rofecoxib users[33] found that 8,199 individuals (0.58%) suffered AMI while using this drug, and thus this drug was withdrawn from the market by the United States Food and Drug Administration (FDA).

Recent studies have reported similar results, thus providing further evidence of the scope and causality of the rebound effect and again calling attention to this type of severe AE.[34,35]

Rebound effects of bronchodilators

Countless studies conducted over the last decades confirmed clinical and experimental findings indicating that "rebound bronchoconstriction", characterized by increased bronchial reactivity and asthma aggravation, might occur following the partial or complete discontinuation of short and long-acting bronchodilators.[5,7,36]

A major randomised clinical trial (26,355 participants) ended prematurely in 2002 after a preliminary analysis pointed to a risk of death by asthma among individuals who were treated with salmeterol (long-acting beta-agonist (LABA)). The results, however, were only published in 2006[37] and reported the occurrence of respiratory-related deaths (RR, 2.16; 95% CI, 1.06-4.41), asthma-related deaths (RR, 4.37; 95% CI, 1.25-15.34), and combined asthma-related deaths or life-threatening experiences (RR, 1.71; 95% CI, 1.01-2.89).

A meta-analysis[38] of 33,826 individuals with asthma who were using LABAs (salmeterol and formoterol) found an increase in exacerbations that required hospitalization (OR, 2.6; 95% CI, 1.6-4.3), life-threatening experiences (OR, 2.1; 95% CI, 1.5-3.0), episodes of fatal asthma (OR, 1.8; 95% CI, 1.1-2.9), and asthma-related deaths (OR, 3.5; 95% CI, 1.3-9.3). The risk of hospitalization did not change despite combining LABA with inhaled corticosteroids (OR, 2.1; 95% CI, 1.3-3.4), thus pointing to the relevance of the rebound effect.

Also, recent meta-analyses[39,40] and a cohort study[41] found similar results, suggesting that knowledge about the paradoxical (rebound) effect and strategies for safe drug use should be mandatory.[42,43]

Rebound effects of antidepressants

Some studies found an increase in depressive symptoms following the partial or complete discontinuation of antidepressants (including selective serotonin reuptake inhibitors (SSRIs)), and related this to a rebound reduction of intra-synaptic serotonin (5-hydoxytryptamine (5HT)) levels due to a downregulation of the post-synaptic receptors. Named in the literature as "serotonin reuptake inhibitor discontinuation syndrome", this syndrome does not depend on the length of treatment nor the type of disease and

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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