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EDUCATION AND DEBATE

Antidepressants, suicidality and rebound effect: evidence of similitude?

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Background: **Samuel Hahnemann noticed that palliative treatments for the symptoms of chronic diseases, after an initial improvement, provoked symptoms similar but stronger symptoms to those initially suppressed. He regarded this as a consequence of the vital reaction of the organism: an automatic and instinctive capacity to return to the initial health condition altered by medicines. Using this homeostatic conception of the organism as a treatment rationale, Hahnemann proposed the therapy of similarity, administering to the patients medicines capable of causing, in healthy individuals, similar symptoms to the natural disease. Based on experimental observations, he proposed that the primary action of the drug was followed by the secondary and opposite action of the organism, inaugurating homeopathic pharmacology, and alerting to the harmful consequences of palliative medicines in susceptible individuals. Such iatrogenic events can be observed in contemporary medicine, after the withdrawal of modern enantiopathic medicines, according to the study of the rebound effect or paradoxical reaction of the organism.**
Method: **This study reviews the recent studies which describe suicidality after the suspension or discontinuation of second generation antidepressants according to the hypothesis of the paradoxical reaction of the organism.**
Conclusions: **Rebound and withdrawal effects, including suicidality occur with antidepressant drugs. They are relatively rare but more intense than the primary action of the drug. The probability of such effects is influenced by patient factors including age and diagnosis, and drug factors including half-life.** *Homeopathy* (2009) **98**, 114–121.

Keywords: similitude; homeopathic medicines; secondary effect; rebound effect; paradoxical reaction; withdrawal syndrome; antidepressant; suicide

Introduction

Similitude law and scientific rationality

In developing the homeopathic doctrine, Samuel Hahnemann maintained a scientific and experimental position, observing effect caused by medicinal substances on the human health, and correlating his observations with evidence from medical literature. In the 'Introduction' of the first edition of the *Organon* (*Organon of the Rational Art of Healing*, 1810), he mentions hundreds of 'examples of accidental homeopathic cure', with dozens of medicinal substances, described by hundreds of doctors citing 247 bibliographical references.

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In the work which incorporated Homeopathy (*Essay on a new principle for ascertaining the curative power of drugs*),[1] using 'analogy' and 'enumeration' of hundreds of pieces of evidence from medical literature, and observed by himself, claiming that through 'strong arguments' he could infer a 'truth or universal law': *a substance is capable of curing symptoms in a sick person, if it causes similar symptoms in healthy people.*

He sketches a physiological explanation for this 'natural law of cure', separating the phenomena, observed in the human experimentation with several medicinal substances, into two different classes, 'primary action of medicines' and 'secondary action or vital reaction of the organism' (*Organon of Medicine*,[2] paragraphs 63–65), systematizing a 'universal action of medicines':

> *"Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed primary*

action. [...] To its action our vital force endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counter-action". (Organon, paragraph 63)

Following these premises and using inductive Aristotelian logic, Hahnemann enunciates the principle of the healing similarity: *every substance capable of causing certain symptoms in healthy people (direct or primary action of the drug), can be used to cure similar symptoms in a sick person, according to the similitude principle (indirect or secondary action of the organism).*

Hahnemann also uses the deductive Aristotelian logic 'modus tollens', 'mode that affirms by denying' or 'indirect proof', to validate the hypothesis of the homeopathic treatment and of the principle of similarity.[3] Denying the effectiveness of enantiopathic treatment in chronic diseases, based as it is in the principle of the contrary (*contraria contrariis curentur*).

Following this 'indirect proof', he mentions numerous examples of substances used according to the principle of contraries, which caused aggravation of the symptoms of the disease, initially suppressed by the treatment (*Organon*, paragraph 59). Hahnemann draws attention to the serious damage that antipathic treatment of chronic diseases can cause to health, triggering *"another, more serious disease or, frequently, incurability, even danger of life and death itself"* (*Organon*, paragraph 60).

I have been described over the last few years, the 'sad results' of the use of modern enantiopathic medicines,[4–10] in accordance with the current pharmacophysiological concepts of 'rebound effect' or 'paradoxical reaction' (secondary action or vital reaction of the homeopathic model).

Vital reaction, secondary action, rebound effect, or withdrawal symptom

In order to understand the 'rebound effect' or 'paradoxical reaction' of the conventional pharmacophysiological model, we must emphasize fundamental aspects of the 'secondary action' or 'vital reaction' of the homeopathic pharmacophysiological model: (1) it appears only in susceptible individuals, who present in their constitution similar symptoms to the pathogenetic effects of the substance; (2) it does not depend on the substance, repetition of the doses or on the type of symptoms (disease); (3) it appears after the primary action of the substance, as an automatic reaction of the organism; (4) it induces an organic state (symptoms) opposite and greater in intensity and/or duration to the primary action of the substance; (5) its effect magnitude is proportional to the intensity of the primary action (dose) of the substance. (*Organon*, paragraphs 59, 64, 69).

In a literature review, Hodding *et al.*[11] described conceptual distinctions, evaluation criteria and scientific evidence of the 'withdrawal syndrome' of some modern drugs (anticoagulants, anticonvulsivants and antipsychotic drugs, barbiturates, benzodiazepines, cimetidine, clonidine, costicosteroids, opiates, propranolol, tricyclic antidepressants etc.). As in other recent revisions, the authors considered the terms 'withdrawal or discontinuation symptoms' as synonym of 'rebound symptoms'. They distinguished the rebound or withdrawal syndrome from the natural evolution of the disease: *"Symptoms resulting from discontinuation of a medication may need to be distinguished from reappearance of disease symptoms or a 'catching up' of the basic disease state, may emerge in the absence of the pharmacological action of the drug"*. They suggest three criteria to confirm a withdrawal symptom: a trial of gradual *versus* abrupt drug termination; the appearance of symptoms more severe than the baseline symptoms; or the onset of symptoms in newborn infants whose mothers had been taking the drug. A gradual tapering of the dose of these drugs is recommended when therapy must be discontinued.

Objectives

(i) To correlate the characteristics of the antidepressants rebound syndrome with the homeopathic vital reaction.
(ii) To describe the scientific evidence relating suicidality to the antidepressants rebound effect.

Material and methods

I reviewed the literature using the Medline database and the keywords 'antidepressant', 'rebound', 'withdrawal syndrome' and 'suicidality', and then selecting the most relevant papers and discussing the scientific evidence.[4–10]

Results

Antidepressants and rebound effect

In the same way as other classes of enantiopathic medicines, antidepressants may trigger a rebound effect of symptoms of depression after the withdrawal of treatment (discontinuation or dose alteration, even single missed doses in susceptible individuals and/or drugs with short half-lifes), with changes in the mediators involved in the process (receptor sensitization and neurotransmitor levels).

In a review on this topic, Wolfe[12] says that antidepressants can cause a variety of withdrawal reactions, *starting within a few days to a few weeks of ceasing to administer the drug and persisting for days to weeks.* Both tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) cause similar syndromes, most commonly characterised by gastrointestinal or somatic distress, sleep disturbances, mood fluctuations and movement disorders. Treatment involves restarting the antidepressant and tapering it more slowly. Some experimental studies confirm the rebound with antidepressants (Table 1).

In a recent review, Lader[21] enhances the understanding of the antidepressant discontinuation syndrome (rebound phenomenon) with additional data: *"The phenomenon has been postulated to be associated with rebound symptoms such as return of depression following abrupt discontinuation. Discontinuation symptoms are now known to be*

Table 1 Examples of experimental studies that confirm the rebound effect of the antidepressants

Drug	*Source*	*Results or conclusions*
	Publication type	
Monoamine oxidase inhibitors (MAOI)	Oniani and Akhvlediani[13] Research support.	After the cessation of the action of the MAOI in cats (suppression of paradoxical sleep and significant decrease in wakefulness), a selective rebound of wakefulness is observed against the background of complete or partial absence of paradoxical sleep.
Clomipramine	Kupfer *et al.*[14] Randomized controlled trial.	Significant drug effects were noted on several sleep parameters, demonstrating suppression of rapid eye movement (REM) sleep. In drug responders were found a significantly faster and more robust rebound in REM sleep than non-responder.
SSRIs	Smith *et al.*[15] Research support.	Animal model (rats) used for studying adaptive changes in the 5-HT(2A) receptor system (serotonergic system, related to SSRIs), showed that a single large dose of quipazine (serotonin receptor agonist) produced a rebound ketanserin-like effect (serotonin receptor antagonist) at 20 h after administration.
Tricyclics	Wolfe[12] Review	Most symptoms related to tricyclic antidepressant withdrawal are believed to be caused by rebound excess of cholinergic activity after prolonged anticholinergic effect on cholinergic receptors (analogous to the adrenergic rebound that occurs after beta-blocker withdrawal).
Fluoxetine	Borrelli *et al.*[16] Randomized controlled trial.	During the on-drug phase, placebo participants gained weight linearly, exceeding the fluoxetine groups. Unlike the placebo group, drug discontinuation produced dose-dependent weight rebound.
Fluvoxamine, Paroxetine	Pace-Schott *et al.*[17] Research support.	Decrease in dream frequency during SSRIs treatment was observed in normal volunteers that may reflect serotonergic REM suppression, while the augmented report length and bizarreness during acute SSRIs discontinuation may reflect cholinergic rebound from serotonergic suppression.
Imipramine	D'Aquila *et al.*[18] Research support.	The results showed that animals treated with chronic imipramine, 40 days after treatment interruption, display a rebound depressive-like behavior (might depend upon parallel changes in the mesolimbic dopamine system sensitivity).
Bupropion	Lerman *et al.*[19] Randomized controlled trial.	Patients who received bupropion are more likely to experience a decrease in depressive symptoms during active treatment but are also more likely to experience a rebound in depressive symptoms when the drug is discontinued.
Olanzapine	Huang *et al.*[20] Research support.	Examining regional changes in rat brain mRNA levels encoding 5-HT(2A) receptor following chronic olanzapine treatment showed immediate effect was a down-regulation of 5-HT(2A) receptor mRNA expression, predominantly in the hypothalamus, limbic system and striatum, while a rebound effect was observed 48 h later. Correlations between 5-HT(2A) receptor mRNA expression and total food intake, weight gain and energy efficiency were observed.

associated with most classes of antidepressants, if medication is stopped without appropriate down-tapering of dose and/or dose frequency. The phenomena associated with stopping almost all antidepressants including the SSRIs are believed to result not from true dependence but from a reduction in intra-synaptic serotonin (5-HT) levels following receptor down-regulation".

This syndrome is characterised by the 'time-locked emergence of new', clearly defined and quantifiable signs and symptoms, which develop on cessation or reduction of an antidepressant that has been taken for more than a few weeks.[22] Typically, patients describe transient symptoms that begin and peak within 1 week of treatment interruption, are mild in severity and follow a finite time-course, usually lasting between 1 day and 3 weeks.[23] In spite of the data from the published literature showing that the incidence of these mild, self-limiting rebound symptoms is generally <5%,[23,24] recent data indicate that a severe and disabling withdrawal syndrome occurs in up to 5% of patients, requiring prompt modification of the management strategy in these idiosyncratic individuals.[25] The literature reveals that paroxetine is associated with a significantly greater proportion of withdrawal reactions (~5%) than the other SSRIs (fluoxetine, for example), with deterioration in various aspects of health and functioning.[23,26–29] The explanation for the difference most likely reflects the long half-life of the main metabolite of fluoxetine, thus acting as a natural taper.[30]

Like in other classes of drugs,[8–10] the rebound reactions are not specific to the particular condition for which the drug is being used, and the antidepressant discontinuation syndrome is similar in incidence, nature and extent throughout depression, panic disorder, generalised anxiety disorder, social anxiety disorder, and obsessive-compulsive disorders (OCDs). Similarly the duration of treatment does not correlate with withdrawal reactions.[31]

In accordance with these studies, the occurrence of the antidepressant rebound phenomenon follows premises similar to the previously mentioned for the secondary action or homeopathic vital reaction: (1) it appears in a small proportion of the people (susceptible or idiosyncratic constitutions)[23–29]; (2) it does not depend on the drug, duration of treatment, type of symptoms or severity of the disease[11,12,21,31]; (3) it appears after the primary effect of the drug, and after discontinuation or alteration of the dose[12,21–23]; (4) it provokes an organic state (symptoms) opposite and greater in intensity and/or duration to the primary action of the drug[11,12,21]; (5) its magnitude is proportional to the intensity of the primary action of the substance, most markedly with the most effective drugs (dose) for suppressing the initial symptoms of the disease.[26–30]

Neurobiological mechanisms of the antidepressant rebound effect

In a review of the neurobiological mechanisms of the antidepressant withdrawal syndrome, Harvey *et al.*[32] proposed a preliminary molecular perspective and hypothesis on the neuronal implications of medication discontinuation, described the evidences that support an association between the antidepressant rebound effect and disturbances in brain glutamate activity, nitric oxide synthesis, and γ-amino butyric acid:

"Inappropriate discontinuation of drug treatment and noncompliance are a leading cause of long-term morbidity during treatment of depression. Increasing evidence supports an association between depressive illness and disturbances in brain glutamate activity, nitric oxide synthesis, and γ-amino butyric acid. Animal models also confirm that suppression of glutamate N-methyl-D-aspartate (NMDA) receptor activity or inhibition of the nitric oxide-cyclic guanosine monophosphate pathway, as well as increasing brain levels of γ-amino butyric acid, may be key elements in antidepressant action. Imaging studies demonstrate, for the most part, decreased hippocampal volume in patients with depression, which may worsen with recurrent depressive episodes. Preclinical models link this potentially neurodegenerative pathology to continued stress-evoked synaptic remodeling, driven primarily by the release of glucocorticoids, glutamate, and nitric oxide. These stress-induced structural changes can be reversed by antidepressant treatment. In patients with depression, antidepressant withdrawal after chronic administration is associated with a stress response as well as functional and neurochemical changes. Preclinical data also show that antidepressant withdrawal evokes a behavioral stress response that is associated with increased hippocampal NMDA receptor density, with both responses dependent on NMDA receptor activation".[32]

The symptoms that follow antidepressant discontinuation include: dizziness, nausea, gastrointestinal distress, headache, gait instability, lethargy, paresthesia, anxiety, irritability, vivid dreams, lowered mood etc. While cholinergic overdrive may explain certain symptoms after tricyclic antidepressants withdrawal, many of these symptoms suggest increased excitability of serotonergic neurons. In the same way that chronic antidepressant treatment results in desensitization of post and presynaptic 5-HT_{1A} receptors, abrupt cessation of 5-HT reuptake inhibition will cause a temporary deficit of available intra-synaptic 5-HT in the face of these down-regulated receptors, resulting in a neurochemical and behavioral pattern caused by loss of inhibitory 5-HT_{1A} mediated synaptic control and an increase in circulating 5-HT.[32,33]

In severe and disabling withdrawal syndrome (5% of patients),[21] overtly raised synaptic 5-HT levels may be detrimental to neuronal function and integrity, enhancing brain glutamate NMDA receptor efficacy. These severe rebound phenomenon are determined by various factors, such as the pharmacological profile of the antidepressant, the time-point and duration of withdrawal, whether withdrawal or noncompliance is repeated and how often, and the impact of associated contributors such as inherent genetic and environmental factors.[32]

Antidepressants and rebound suicidality

My initial hypothesis is that the enantiopathic treatment of the symptoms of the depression with second generation antidepressants, after the withdrawal (discontinuation or dose alteration), provokes a significant worsening of the depression symptoms initially suppressed (for example, suicidal ideation, suicidal attempts or suicidal behavior), as a consequence of the rebound effect or paradoxical reaction of the organism.

In the most comprehensive meta-analysis to investigate the relationship between antidepressant drugs and suicidality in pediatric patients in placebo-controlled trials, Hammad *et al.*[34] included all studies submitted to the Food and Drug Administration (FDA). The evaluated data were derived from 4582 patients in 24 trials comprising 23 trials conducted by 9 drug companies (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, bupropion, venlafaxine, nefazodone and mirtazapine) and 1 multicenter trial (TADS)[35] that evaluated only fluoxetine. Sixteen trials studied patients with major depressive disorder (MDD), 4 trials studied patients with OCD, and 4 trials studied patients with non-obsessive-compulsive anxiety disorder (non-OCD anxiety). Only 20 trials were included in the risk ratio (RR) analysis of suicidality because 4 had no events in the drug or placebo groups. The multicenter trial (TADS) was the only individual trial to show a statistically significant RR (RR 4.62; 95% CI, 1.02–20.92). The overall RR for SSRIs in depression trials was 1.66 (95% CI, 1.02–2.68) and for all drugs throughout all indications 1.95 (95% CI, 1.28–2.98). The overall risk difference (RD) for all drugs within all indications was 0.02 (95% CI, 0.01–0.03). The FDA concluded that these medications pose a 2-fold (4% verum *versus* 2% placebo) increased risk for 'suicidal behavior' or 'suicidal ideation', a modestly increased risk of suicidality.

In the FDA analysis, suicidal behavior comprised actual suicide attempts and preparatory actions toward imminent suicidal behavior; suicidal ideation was defined as passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior.

In a recent meta-analysis[36] to assess the efficacy and risk in reported suicidality (occurrence of suicidal ideation, suicidal attempt or suicidal behavior) of antidepressant treatment for pediatric disorders, 27 randomized controlled trials of pediatric antidepressant treatment were selected (MDD = 15; OCD = 6; non-OCD anxiety = 6), and RDs for response and for suicidal ideation/suicide attempts estimated by the random-effect methods. Pooled RDs in rates of primary study-defined measures of responder status significantly favoured antidepressants for MDD (RD 11.0%; 95% CI, 7.1–14.9%), OCD (RD 19.8%; 95% CI, 13.0–26.6%), and non-OCD anxiety disorders (RD 37.1%; 95% CI, 22.5–51.7%). There was increased RD of suicidal ideation/suicide attempt in all

trials and indications for drug *versus* placebo [RD 0.7%; 95% CI, 0.1–1.3% (number needed to harm, 143, 95% CI, 77–1000)], the pooled RDs within each indication were not statistically significant: MDD (RD 0.9%; 95% CI, −0.1% to 1.9%), OCD (RD 0.5%; 95% CI, −1.2% to 2.2%), and non-OCD anxiety disorders (RD 0.7%; 95% CI, −0.4% to 1.8%). There were no completed suicides. Age-stratified analyses showed that for children younger than 12 years with MDD, only fluoxetine showed any benefit over placebo. With the placebo as a reference point, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. The relationship among the rates of treatment of emergent suicidality, antidepressant groups (verum and placebo) and the disorders is shown in Table 2.

Similar to the FDA's analysis, Hammad *et al.* found an overall increased risk of suicidal ideation/suicide attempt associated with antidepressant treatment.[34] In conventional analysis,[37] several factors may contribute to rates of suicidality in randomized antidepressant clinical trials: (1) recruitment of acutely depressed subjects early in an episode, when suicidal risks are especially high; (2) adverse selection of less treatment-responsive depressed patients into trials; (3) intensive monitoring for adverse events, including suicidal thoughts; (4) delay of antidepressant effects; (5) evident lack of a suicide risk-reducing effect of short-term antidepressant treatment; (6) unrecognized, antidepressant-induced mixed or psychotic states, particularly in misdiagnosed bipolar disorders; and (7) rate (events per time) inflation based on identifying suicidal events in brief time samples early in acute depressive illnesses.

Table 2 Relationship among the rates of treatment emergent suicidality, antidepressant groups (verum and placebo) and the disorders[36]

Drug (pooled trials estimates)	*Rate of suicidality*		*RD % (95% CI)*
	No. of events/total (%)		
	Verum	*Placebo*	
MDD			
Fluoxetine	17/287 (6)	11/289 (4)	2 (−3 to 6)
Paroxetine	12/377 (3)	4/285 (1)	2 (−1 to 4)
Sertraline	5/189 (3)	2/184 (1)	2 (−1 to 4)
Citalopram/ Escitalopram	11/348 (3)	9/338 (3)	0 (−3 to 2)
Venlafaxine	8/182 (4)	0/179 (0)	4 (1 to 8)
Nefazodone	0/279 (0)	0/189 (0)	0 (−1 to 1)
Mirtazapine	1/170 (1)	0/89 (0)	1 (−2 to 3)
OCD			
Fluoxetine	1/86 (1)	0/46 (0)	1 (−4 to 6)
Fluvoxamine	2/57 (4)	0/53 (0)	4 (−2 to 9)
Paroxetine	1/99 (1)	0/107 (0)	1 (−2 to 4)
Sertraline	0/120 (0)	1/123 (1)	−1 (−4 to 2)
Non-OCDs anxiety			
Fluoxetine	0/37 (0)	0/37 (0)	0 (−5 to 5)
Fluvoxamine	0/63 (0)	0/65 (0)	0 (−3 to 3)
Paroxetine	3/165 (2)	0/156 (0)	2 (−1 to 4)
Sertraline	0/11 (0)	0/11 (0)	0 (−16 to 16)
Venlafaxine	3/297 (1)	1/313 (0)	1 (−1 to 2)

Important aspects can be related with the probable hypothesis of the withdrawal syndrome or rebound effect:[36] *age-stratified analyses showed that for adolescents with MDD, only fluoxetine showed benefit over placebo the largest effectiveness of the drug may relate to its long half-life (more than 5 days); among adolescent participants treated with placebo, the risk of suicidal ideation/suicide attempt was greater in MDD trials compared with non-OCD anxiety disorders trials (odds ratio 9.9; 95% CI, 1.6–406.3) and OCD trials (odds ratio 5.8; 95% CI, 0.9–237); the multicenter trial (TADS), that evaluated only fluoxetine in MDD, to show a greater RD of suicidality (RD 7%; 95% CI, 1–12%).*

The epidemiology, clinical course and antidepressant treatment of MDD present other relevant aspects[38] for the argument of the relationship between suicide and rebound effect (withdrawal reaction): *suicidal thinking and attempts are more common in depressed adolescents (35–50% will attempt suicide, and 2–8% will complete suicide over a decade); the risk of new-onset of suicidal behavior is greatest in the first 2 weeks of treatment and in adolescents with their first episode of depression (86% of all TADS participants); compared with adults, youths who take antidepressants have an increased risk of behavioral activation, hypomania or mania, new-onset suicidal thoughts and behaviors.*

It is important to stress that the adverse events assessed in these meta-analysis[34,36] were only those that occurred during the double-blind acute treatment period (4–16 weeks) or within 1 day of the end of this period, underestimating the rebound effect of the antidepressant drugs with larger half-life longer than 24 h (fluoxetine, for example). By definition,[11,12,21] main rebound effects of the organism happen after withdrawal of enantiopathic treatment, with decreased drug concentration and the consequent partial or total vacating of the receptors, allowing the manifestation of the paradoxical reaction of the organism, producing symptoms of greater intensity than those initially suppressed by palliative drugs. One cannot observe the real magnitude of the rebound phenomenon if the minimum time (half-life) for the total metabolisation of the drug is not taken into account?

These aspects support the physiopathological hypothesis that relates the exacerbation of the depressive symptoms (suicidality) with the rebound effect (secondary action or vital reaction) of the organism, after antidepressants withdrawal (Table 3).

On May 2nd, 2007, the FDA proposed that makers of all antidepressant medications update the existing black box warning on their products' labeling to include warnings about increased risks of suicidality in young adults (ages 18–24) during initial treatment (generally the first one to two months). The FDA reached its conclusions after a comprehensive review of 295 individual antidepressant trials that included over 77,000 adult patients with MDD and other psychiatric disorders. The analysis found no increased risk of completed suicides in patients taking the medications, but 21 suicide attempts were reported among the 3810 participants of 18–24 years of age: an incidence of 0.55%, twice the risk of individuals of the same age who took placebo.[39]

Current estimates suggest that 3 million Americans in this age group received at least one prescription for an

Table 3 Relationship between rebound effect (vital reaction) and suicidal risk with antidepressant drugs

Rebound effect	*Suicidal risk with antidepressant drugs*
Appears in a small proportion of the people (susceptible or idiosyncratic constitutions).	Compared with adults, youth who take antidepressants have an increased risk of behavioral activation, hypomania or mania, and new-onset suicidal thoughts and behaviors.
Does not depend on the drug, duration of treatment, type of symptoms or severity of the disease.	Risk of increased suicidal behavior with any antidepressant is highest during the first weeks of treatment; risk of new-onset suicidal behavior is greatest in adolescents with their first episode of depression.
Appears after the primary effect of the drug on discontinuation or alteration of the dose.	Risk of increased suicidal behavior with any antidepressant is highest if the dosage is increased or decreased.
Provokes an organic state (symptoms) opposite and greater in intensity and/or duration to the primary action of the drug.	Suicidal thinking and attempts are more common in depressed adolescents; among adolescents treated with placebo, the risk of suicidal ideation/suicide attempt was greater in MDD trials compared with other conditions.
Magnitude is proportional to the intensity of the primary action most markedly with the most effective drugs (dose) for suppressing the initial symptoms of the disease.	For adolescents with MDD, only fluoxetine showed benefit over placebo, it has the longest half-life of SSRIs. Fluoxetine in MDD, shows a greater RD of suicidality.

antidepressant per year, we could infer that 16,500 young adults treated with antidepressants in the USA might exhibit suicidal thinking or behavior.

Discussion

In the same way as with the non-steroidal anti-inflammatory drugs (NSAIDs)[9] and long-acting bronchodilator drugs (LABA),[10] in this study I sought new evidence of the relationship between antidepressants and suicide.[8]

The most common explanation for this phenomenon is the 'syndrome of activation', where the antidepressant produces psychomotor improvement prior to mood improvement, but this hypothesis does not apply to all studies, because the suicidal tendency was observed throughout treatment, mainly when the dose is changed.

It has also been postulated that serotonin (5-HT) is a modulator, which modulates the homeostasis between dopamine, noradrenaline and γ-amino butyric acid (GABA), which mediate the thought processes, anxiety and mood, respectively. When this homeostasis gets disturbed, depression occurs. The therapeutic mechanism of action of serotonergic drugs (SSRIs) involves an alteration in the 5-HT system and inhibition of the neuronal uptake pump of serotonin. The plethora of biological substrates, receptors and pathways for 5-HT are candidates to mediation not only of the therapeutic actions of SSRIs, but also of their side effects. A hypothesis to explain these immediate side effects is that 5-HT is increased at specific 5-HT receptor subtypes in discrete regions of the body where the relevant physiologic processes are regulated.[40]

In 5% of the patients,[21] these stress-induced neurochemical changes promote events with insidious and malignant implications for the outcome of the depression, as a consequence of the increase in brain glutamate activity and nitric oxide synthesis, and decrease in amino butyric acid levels. These disturbances alter the expression of critical cellular resilience proteins and synaptic plasticity, changing the neuronal response.[32]

I postulate that suicidality, observed on discontinuation of SSRI treatment in individuals with MDD and more susceptible to the primary actions of these medicines and after the suspension or alteration in the dosage of the drug, are due to the vital reaction or rebound effect of the organism, promoting a depletion of intra-synaptic 5-HT levels after an initial rise.

Arguing against this hypothesis, Jeffrey *et al.* comment in their meta-analysis[36]: "*While there has been some speculation that an emergent suicidal ideation/suicide attempt might be induced by withdrawal effects found particularly in those drugs with shorter half-lives, we found no such association when comparing the risk of suicidal ideation/suicide attempt in fluoxetine, a drug with a longer half-life (5 days) than those of the other drugs (all substantially shorter than 24 h) (P = 0.58). Furthermore, the risk of incident suicidal ideation/suicide attempt does not appear to be a consequence of lack of efficacy, insofar as the size of increased risk is as similar for anxiety as it is for depression in adolescents, even though antidepressants are more efficacious for anxiety than for depression*".

But this disregards the premises of the rebound effect: the magnitude of the rebound effect and not to the 'lack of efficacy' as the authors suppose. A longer period of observation after the suspension of fluoxetine should be considered, if we want to evaluate the real magnitude of the rebound effect.

In spite of the low effectiveness of the antidepressants in MDD, the largest suicidality risk is observed in this group because suicidal symptoms are more common in MDD than in the other analyzed disorders (OCD and non-OCD anxiety). The magnitude of the rebound effect is proportional to the intensity of the primary action of the substance, presenting the most evident reactions in the drugs most effective in suppressing the initial symptoms of the disease.

In other words, the severe and disabling antidepressant withdrawal syndrome is only observed in constitutions susceptible to the enantiopathic effect of the medicine, and when the symptoms of the disease are efficiently suppressed by its primary action. They are not observed in disorders (OCD and non-OCD anxiety) since the direct and strong relationship doesn't exist between the natural symptoms of the disease (suicidality) and the contrary action of the

drug (anti-suicidality). Hahnemann enunciated this two hundred years ago:

> *"During the primary action of the artificial morbific agents (medicines) on our healthy body, as seen in the following examples, our vital force seems to conduct itself merely in a passive (receptive) manner, and appears, so to say, compelled to permit the impressions of the artificial power acting from without to take place in it and thereby alter its state of health; it then, however, appears to rouse itself again, as it were, and to develop (A) the exact opposite condition of health (counteraction, secondary action) to this effect (primary action) produced upon it, if there be such an opposite, and that in as great a degree as was the effect (primary action) of the artificial morbific agent on it, and proportionate to its own energy; or (B) if there be not in nature a state exactly the opposite of the primary action, it appears to endeavor to indifferentiate itself, that is, to make its superior power available in the extinction of the change wrought in it from without (by the medicine), in the place of which it substitutes its normal state (secondary action, curative action)". (Organon*, paragraph 64)

To confirm causality between suicidality and the antidepressants rebound effect, described in previous studies for other depressive symptoms, new clinical trials need to be conducted, prioritizing the initial changed of mood (primary action) and the side effects (secondary action) that occur in a longer period after the suspension of the drugs, so that the rebound effect (secondary action) of the organism can fully manifest itself.

Compared to the studies of other drugs (NSAIDs and LABA),[9,10] certain analogies with the antidepressant rebound phenomenon can be observed:

(i) Rebound symptoms are much more intense than the symptoms initially suppressed by the primary action of the enantiopathic drugs;

(ii) Although they affect a small percentage of the individuals (idiosyncratic constitutions), fatal rebound events assume epidemic importance when we consider the level of consumption of medicines by the population: long-acting β-agonists (LABA) cause approximately 1 death per 1000 patient-years of use (4000–5000 asthma-related deaths a year in the USA alone); SSRIs cause approximately 5 suicidality episodes per 1000 young adult patient-years of use (16,500 episodes of suicidal thinking or behavior per year in the USA alone);

(iii) In controlled studies, compared to placebo, the risk of ischemic fatal events was 3.4 times higher after the suspension of aspirin, 1.52 times higher after the suspension of non-selective NSAIDS and 1.67 times higher after the suspension of rofecoxib; the risk of fatal bronchoconstriction was 2–4 times higher after the suspension of LABAs; the risk of suicidality was 6 times higher after the suspension of the short half-life SSRIs;

(iv) The time of manifestation of the paradoxical reaction after the suspension of the treatment was similar across the different classes of drugs: 10 days for aspirin, 14 days for NSAIDs, 9 days for rofecoxib and 7 days for antidepressants;

(v) Duration of the treatment was not directly related to the manifestation of the rebound effects;

(vi) Drugs with stronger enantiopathic effects suppress the primary symptoms of the disease more intensely, triggering proportional greater paradoxical reactions.

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