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The Clinical Meaning of Withdrawal with Antidepressant Drugs

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Thirty years ago, in this journal, I published an editorial [1] that, for the first time, discussed clinical issues that were going to achieve wide currency only two decades later. I wondered whether time had come "for debating and initiating research into the likelihood that psychotropic drugs actually worsen, at least in some cases, the progression of the illness which they are supposed to treat" [1, p. 125]. The paper was based on a number of clinical observations I had made over the years in my clinical practice; a substantial part was concerned with antidepressant drugs [1]. My own clinical observations on withdrawal syndromes, loss of clinical effect during long-term treatment, resistance, and iatrogenic psychological changes ensuing with these medications were discussed with the scanty literature that was available [1]. The editorial reflected my clinical conviction that all these phenomena were related and probably part of the same neurobiological process. The manifestations were different, but they tended to cluster together and to occur almost exclusively after the initial phase of treatment. For instance, a patient is doing well with long-term antidepressant treatment, yet, at a certain point, without any major events and despite good adherence, starts having symptoms of a depressive relapse. I may increase the dosage of the antidepressant, but with transient symptom relief. If I switch the patient to a different medication, a withdrawal syndrome, consisting of symptoms the patient had never experienced before, is likely to occur and the patient is unlikely to respond to the new antidepressant. All these phenomena were reported also by a number of investigators, but their actual meaning appeared to be unclear [1]. My clinical impression was that something happens in the progress of treatment, but I did not have any idea of what could be its neurobiological substrate.

The editorial had a long incubation time (almost a year), with exchanges with a few experts in the field whom I felt could be receptive to the problem. The intellectual process is very unlikely to occur today: starting from clinical observations, collecting histories and data, referring to existing literature, reflecting on the issues, formulating tentative hypotheses and testing them with the patients whom I had seen before. Today most of the researchers are unfamiliar with the clinical process and do not wish to acknowledge that a seasoned clinician examining a patient is not getting the same information of a research assistant using a checklist [2]. When the editorial appeared in 1994 [1], I sent the reprint around (pdf files were just starting then), eager to get some feedback. I was lucky to get a reply from an eminent psychopharmacologist, Baldessarini [3], who wrote an editorial commenting on my hypotheses. He particularly discussed the relationship between antidepressant medications and bipolar disorder (e.g., the phenomenon of switching) and the potential implications of rapid versus slow

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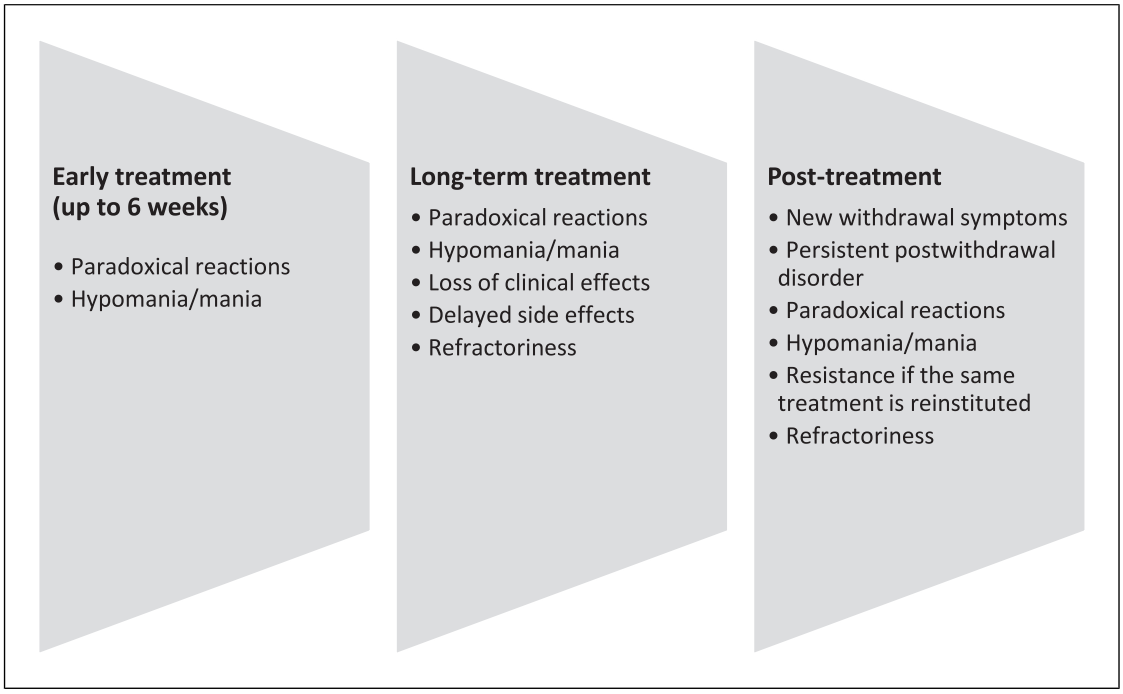

Fig. 1. The oppositional model of tolerance applied to antidepressant medications.

discontinuation of psychotropic drugs [3]. He concluded that the editorial writer was "not alone in wondering about the risks involved in the long-term use of psychotropic agents, and particularly in their discontinuation" [3, p. 140]. Not feeling alone was indeed important for me personally at that time. A number of clinicians who wrote personal letters stating that they had seen the same clinical phenomena provided an additional source of support.

I was still looking, however, for a model that might provide a link and a pathophysiological explanation for the clinical phenomena that were discussed [1, 3]. Pharmacodynamic tolerance was on the top of my suspicions. When I received the new edition of a psychopharmacology textbook, I jumped to read the chapter written by Young and Goudie [4] on the adaptive processes regulating tolerance to behavioral effects of drugs. They emphasized the importance of differentiating between dispositional (pharmacokinetic) tolerance, which reduces the concentration of a drug or its duration of action, and functional (pharmacodynamic) tolerance, which changes sensitivity to a drug [4]. Continued drug treatment may recruit processes that oppose the initial effect of a drug or of a receptor; when drug treatment ends, these processes may operate unopposed, at least for some time [4]. This oppositional model of tolerance was a perfect fit for my clinical observations and I felt I could apply it to antidepressant drugs in an editorial that I published in 1995 [5]. The model was subsequently refined in 2003 [6], when I collected the literature that supported or rejected this assumption. Its most updated version is described in a book I recently published [7]. The oppositional model of tolerance (Fig. 1) may explain loss of treatment efficacy during maintenance treatment and the fact that some side effects tend to occur only after a certain time. These processes may also shift the illness into a treatment-unresponsive course, or into bipolar or paradoxical manifestations. When drug treatment ends, oppositional processes no longer encounter resistance, resulting in potential onset of new withdrawal symptoms, persistent post-withdrawal disorders, hypomania, resistance to treatment if it is reinstituted and refractoriness [5–7]. I concluded my editorial in 1995 [5] remarking that researchers working along these lines were likely to encounter tremendous difficulties in performing their studies and getting them funded and published. I hoped, however, that our readers and contributors could support our independent journal, at that time "alone in its battle for opening a new research paradigm" [5, p. 60]. This paper is an account of the 30-year journey that ensued and of the clinical insights that I progressively gained.

The Clinical Challenge of Discontinuing Antidepressant Medications

In the mid-nineties, as other clinicians, I was confronted with the phenomenon of withdrawal syndromes occurring during tapering and/or discontinuation of selective serotonin reuptake inhibitors (SSRI). Such manifestations were subsequently found to occur also with serotonin-noradrenaline reuptake inhibitors (SNRI). These phenomena were clearly more severe and frequent than those occurring with previous antidepressant medications. The term "withdrawal syndrome" that was initially used was soon substituted by "discontinuation syndrome," in guidelines and reviews, which were heavily influenced by the pharmaceutical industry. The aim of this commercial operation was to reinforce the conviction that these problems were devoid of important clinical implications and could be prevented by gradual tapering. Both physicians and patients were taught that the problem manifests itself only with abrupt discontinuation of antidepressant medications and that, if symptoms arise, they have to be considered signs of relapse, with prompt readministration of the antidepressant [7].

Many clinicians, in all specialties and types of practice, were able to perceive there was something wrong with the approach dictated by the pharmaceutical industry and its prodigal experts. However, they were reluctant to voice that the emperor had no clothes because the scientific literature was compact, with very few exceptions, in praising the emperor's clothes. The wall of denial built by the pharmaceutical industry and special interest groups was overcome by systematic reviews that were published about two decades later [8–10]; two of them [8, 9] appeared in this journal. These papers clarified that: (a) withdrawal symptoms may occur also with slow tapering; (b) symptoms may be severe and may persist over months or years; (c) there are no substantial differences in clinical manifestations of withdrawal between antidepressant drugs and other psychotropic medications (and thus the term "withdrawal syndrome or symptom" is appropriate). In 2015, in this journal [11], Guy and Virginie-Ann Chouinard outlined clear definitions of "relapse/recurrence," "new withdrawal symptoms," and "persistent postwithdrawal disorder": relapse and recurrence are the gradual return of the original symptoms at the same intensity as before treatment, entailing a return of the same episode and a new episode of illness, respectively; new withdrawal symptoms are classic withdrawal symptoms that are new and not part of the patient's original illness; persistent post-withdrawal disorder occurs when symptoms are protracted and/or there is return of the original illness at a greater intensity and/or symptoms are related to emerging new disorders.

As a clinician, I happened to be, from the very beginning, in the front line. Tapering and discontinuing antidepressants were part of the sequential approach that characterized our affective disorders program and I personally handled all cases [12]. Further, I was consultant to many skillful clinical psychologists who treated anxiety disorders with cognitive behavior methods and Well-Being Therapy [13]; when their patients recovered they expected me to discontinue antidepressant drugs that were no longer deemed to be necessary [12]. Contrary to their expectations, my job was not easy, as we also demonstrated in a trial years later [14]. As a result, my personal experience with discontinuing antidepressant medications became very extensive (hundreds of patients over the years). I am not ashamed to state that insights occurred very slowly, after years of practice, reflections, and readings.

I soon realized that discontinuing SSRI and SNRI was a difficult and complex task. If we expect withdrawal symptoms in about 1 patient out of two [8–10], it would be helpful to be able to identify who is likely to develop them. Unfortunately, I was not able to infer any consistent clue, except a higher risk when paroxetine and venlafaxine were involved. I also realized that guidelines suggesting an approach to be used in all cases were totally inadequate, if not ridiculous. There were so many different situations that could be faced. Examples are improved clinical conditions of a patient; lack of indications for the initial prescription (particularly from primary care physicians); need to change antidepressant because of lack of efficacy; medical side effects [7]. Initially, I attempted to taper antidepressants at the slowest possible rate, with the idea that the very low occurrence of withdrawal reactions I had found with tricyclic antidepressants [12] could be due to the small decrements that were feasible with those medications (25 mg every other week). However, my results with SSRI and SNRI were disappointing and I thought that I needed to explore other roads.

A clinician's experience is very much based on the type and accuracy of clinical assessment, that is on the quality of data that are collected [2]. My assessment of psychiatric symptomatology is very much influenced by Paykel's Clinical Interview for Depression [15]. One item of the scale is concerned with reactivity to social

environment (changes in mood and symptomatology in direction of either improvement or worsening as a result of environmental circumstances). I realized that most of the patients in the tapering phase displayed high vulnerability to surrounding events and such vulnerability increased after discontinuation. I discussed this observation with Guy Chouinard, who suggested me to add a medication with neuroprotective properties to support the person during that phase. I chose clonazepam because of its antianxiety and antiepileptic properties, paucity of side effects, facility to titrate, lack of significant interactions, mood modulating effects, and low likelihood of dependence compared to other benzodiazepines [16]. I thus started adding clonazepam to the antidepressant I wanted to discontinue and, after 2 weeks of stabilization, I began tapering [7]. Clonazepam could be increased when withdrawal symptomatology worsened. As withdrawal symptomatology may persist for months and build up into post-withdrawal disorders, also clonazepam treatment may be protracted [7]. I was concerned that I might substitute one dependence (antidepressant) with another (clonazepam), but, using slow tapering of clonazepam [16], I did not encounter a single case where problems occurred. Another characteristic of my assessment was my attention to potential iatrogenic factors that are often neglected by physicians in all specialties [17]. In addition to checking withdrawal and post-withdrawal symptoms, in the clinical history I was looking for episodes of paradoxical effects, switching, loss of clinical effect despite adequate adherence, lack of response to a previously effective antidepressant treatment when it is started again after a drug-free period [6, 7]. In part of my cases, I found an association with these events. I thus built a staging method for rating the occurrence and extensions of such manifestations [7, 18]. In a few patients, I observed that withdrawal symptoms did not occur the first time a specific antidepressant was used but ensued at a later point in time after the occurrence of events related to the model of oppositional tolerance (Fig. 1).

An important source of learning came from paying attention to the individual attitudes and behavior that shape the perception and presentation of withdrawal symptoms, the interactions between patients and physicians, and the response to treatment [19]. Over the years, I have realized the importance of shifting the patient from his/her passive role of consumer to health producer by the use of self-therapy that may be facilitated by psychotherapy [20]. A key aspect of management is thus that of providing an explanation for what is happening, information for what we can reasonably expect, and a plan for overcoming the situation.

Sharing the Meaning of Withdrawal Symptomatology

Shared decision making is a cornerstone of current medical practice [21]. A major difficulty in its implementation is to provide an understandable description of the pathophysiological processes and of the ensuing treatment options. An increasingly popular model for antidepressant drugs [22] is pharmacokinetic and suggests very small decrements of the antidepressant, particularly in the doses approaching discontinuation, in a process that may take months or years. These very small decrements may be achieved with liquid formulations or with personalized tapering strips. The superiority of this ultra-slow tapering, however, has not be supported by adequate randomized controlled trials. Further, the pharmacokinetic model is unable to explain a number of clinical phenomena that are associated with antidepressant drug reduction or discontinuation, such as the very wide range of severity of withdrawal that does not necessarily reflect the pharmacokinetic characteristics of the medications; the occurrence of persistent post-withdrawal disorders; the associated modifications of the illness course (e.g., onset of hypomania, loss of clinical effects, and refractoriness to treatment) [8, 9]. On the contrary, as a clinician, I have found that the oppositional model of tolerance that was based on pharmacodynamic principles, is very helpful for understanding and addressing all clinical phenomena related to antidepressant drugs withdrawal manifestations [5–7]. The model views withdrawal syndromes as one of the possible manifestations of behavioral toxicity, i.e., the pharmacological actions of a drug that, within the dose range in which it has clinical utility, may produce alterations in mood, perceptual, cognitive, and psychomotor functions that limit the capacity of the individual or constitute a hazard to his/her well-being [23, 24]. Behavioral toxicity, in addition to withdrawal symptomatology, may manifest with switch to hypomania and bipolar course, loss of treatment effect, refractoriness to a treatment which was effective in the past, paradoxical responses (e.g., deepening of depression) [24]. If we adopt this line of interpretation, the sooner we are able to discontinue the antidepressant medication, the better, whereas very slow tapering is likely to prolong exposure to an agent that has become toxic to the individual. It is important to discuss with the patient the different options that may be

available in the specific case. There are clinical situations where a sudden or very rapid discontinuation is indicated (e.g., change of medications, medical side effects such as gastric bleeding, a patient who has just started taking an antidepressant that was inappropriately prescribed). In other situations, a slower pace of discontinuation (but not exceeding a couple of months in most cases), with clonazepam as an adjuvant, may be discussed with the patient. Most of my patients were pushing for getting rid of the antidepressant as soon as possible and were ready to endure withdrawal symptoms that might have occurred. The concept of behavioral toxicity may thus provide a strong motivational element for patients.

It is then important to outline the essential role of self-therapy that can be enhanced by specific psychotherapeutic strategies (explanatory therapy, cognitive behavioral therapy, Well-Being Therapy), in the entire process [7, 12]. I have always disliked the term "deprescribing" since it implies that the use of medications was unwarranted and can simply be subtracted from the treatment. For instance, a young female patient is prescribed an antidepressant for panic attacks that makes her feel better. However, now, after many years of treatment, she wants to discontinue it because she plans to get pregnant. It is then clear that deprescribing, without the substitution of the medication with appropriate self-therapy, would carry a very high risk of relapse [7, 12]. If patients have a long history of struggles with antidepressant discontinuation and behavioral toxicity (particularly post-withdrawal disorders that have lasted years), they are likely to believe that their disturbances are irreversible and the situation is hopeless. Over the years, I have learned that unwarranted optimism ("everything will be fine") may only set the stage for further disillusionment and frustration. I thus prefer to say: "We know so little about these disturbances, because they have been ignored by research, and I have to rely on my clinical experience on hundreds of cases. What I have observed is that when patients have been able to stay away from any type of antidepressant medications, while continuing therapy with clonazepam, and endorsed the self-therapy I suggested, in due course (months or years), these disturbances decreased their intensity and faded. We will try this approach also in your case."

Conclusion

The meaning that we attribute to withdrawal syndromes ensuing during tapering and/or discontinuation of antidepressant medications is likely to influence a clinician's approach, the patient-doctor relationship, and the final outcome. We may view withdrawal syndromes as isolated, self-limiting manifestations, which in due course and with the appropriate tapering methods subside, totally unrelated to other manifestations of behavioral toxicity. The hidden conceptual assumption is that the patient's condition will go back to a premorbid state that is the receptor changes that are induced by antidepressants are limited to their time of administration or shortly afterward and that it is just a matter of allowing time for adaptation of the system to antidepressant discontinuation. The process is purely pharmacological and does not require the active participation of the patient, who remains, because of the prolonged time required by tapering, a faithful consumer. No threat to commercial interests. Alternatively, we may view withdrawal symptomatology as part of a more general problem related to the use of antidepressant medications (Fig. 1). The priority then becomes to stop exposure to antidepressant medications as soon as possible. Using current concepts on the plasticity of the brain [25], recovery from withdrawal and post-withdrawal disorders is viewed as a one-way street, characterized by structural remodeling of neural architecture and continually changing patterns of gene expression mediated by epigenetic mechanisms. Patients are asked to be active participants in the process of recovery (health producers), instead of being simply consumers. Such processes may be facilitated by the use of psychotherapeutic strategies [7, 12]. The view poses major threats to commercial interests since it limits the use of antidepressant drugs to the most severe cases of depression and for the shortest possible time, and challenges their use in anxiety disorders unless a depressive illness coexists [7].

Thirty years after the publication of my editorial [1], I am pleased to see that it has stimulated clinical and research considerations. However, many of the questions that were raised [1] are still unanswered and cannot be addressed by an oversimplified psychiatry brainwashed by the pharmaceutical industry. What many psychiatrists have learnt is to perform a diagnosis according to DSM and to write one or more prescriptions in an automatic fashion [2]. A problem is that the DSM applies to patients who no longer exist (drug-free subjects): most of the patients who come to clinical observation today are already taking psychotropic drugs and this occurrence is likely to affect the presentation and outcome of symptoms [24]. Yet the iatrogenic perspective is more than just ignored: it is forbidden. The behavioral toxicity of antidepressant

medications is a major healthcare problem that needs to become a priority for research and funding. Helping patients to overcome their difficulties in discontinuing antidepressant medications requires excellent skills in differential diagnosis; deep knowledge not only of the potential benefits of treatments (antidepressant drugs remain life-saving medications in severe depression), but also of their vulnerabilities; and awareness of the advances in psychotherapy that enable self-therapy. We also need psychiatrists who are able to understand that each individual case may be different (one size does not fit all) and to use clinical judgment for a better understanding of phenomena [7].

Conflict of Interest Statement

Giovanni A. Fava has written a book on discontinuing antidepressant medications [7], for which he receives royalties. He has no other financial conflicts of interest to declare.

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Author Contribution

Giovanni A. Fava conceived and wrote the entire manuscript.

References

1 Fava GA. Do antidepressant and antianxiety drugs increase chronicity in affective disorders? Psychother Psychosom. 1994;61(3–4):125–31. https://doi.org/10.1159/000288880
2 Balon R. The checklist psychiatrist. Psychother Psychosom. 2024;93(3):151–4. https://doi.org/10.1159/000538544
3 Baldessarini RJ. Risks and implications of interrupting maintenance psychotropic drug therapy. Psychother Psychosom. 1995;63(3–4):137–41. https://doi.org/10.1159/000288950
4 Young AM, Goudie AJ. Adaptive processes regulating tolerance to behavioral effects of drugs. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology. New York: Raven Press; 1995. p. 733–42.
5 Fava GA. Holding on: depression, sensitization by antidepressant drugs, and the prodigal experts. Psychother Psychosom. 1995;64(2):57–61. https://doi.org/10.1159/000288992
6 Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? J Clin Psychiatry. 2003;64(2):123–33. https://doi.org/10.4088/jcp.v64n0204
7 Fava GA. Discontinuing antidepressant medications. Oxford: Oxford University Press; 2021.
8 Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. Psychother Psychosom. 2015;84(2):72–81. https://doi.org/10.1159/000370338
9 Fava GA, Benasi G, Lucente M, Offidani E, Cosci F, Guidi J. Withdrawal symptoms after serotonin-noradrenaline reuptake inhibitor discontinuation: systematic review. Psychother Psychosom. 2018;87(4):195–203. https://doi.org/10.1159/000491524
10 Davies J, Read J. A systematic review into the incidence, severity, and duration of antidepressant withdrawal effects: are guidelines evidence-based? Addict Behav. 2019;97:111–21. https://doi.org/10.1016/j.addbeh.2018.08.027
11 Chouinard G, Chouinard VA. New classification of selective serotonin reuptake inhibitor withdrawal. Psychother Psychosom. 2015;84(2):63–71. https://doi.org/10.1159/000371865
12 Fava GA, Belaise C. Discontinuing antidepressant drugs: lesson from a failed trial and extensive clinical experience. Psychother Psychosom. 2018;87(5):257–67. https://doi.org/10.1159/000492693
13 Fava GA; Well-Being Therapy. Treatment manual and clinical applications. Basel, Karger; 2016.
14 Fava GA, Bernardi M, Tomba E, Rafanelli C. Effects of gradual discontinuation of selective serotonin reuptake inhibitors in panic disorder with agoraphobia. Int J Neuropsychopharmacol. 2007;10(6):835–8. https://doi.org/10.1017/S1461145706007462
15 Paykel ES. The clinical interview for depression. Development, reliability and validity. J Affect Disord. 1985;9(1):85–96. https://doi.org/10.1016/0165-0327(85)90014-x
16 Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal and rebound. J Clin Psychiatry. 2004;65(Suppl 5):7–12.
17 Fava GA, Rafanelli C. Iatrogenic factors in psychopathology. Psychother Psychosom. 2019;88(3):129–40. https://doi.org/10.1159/000500151
18 Fava GA. Clinical use of staging in psychiatry. Psychother Psychosom. 2024;93(3):143–50. https://doi.org/10.1159/000538526
19 Fava GA, Cosci F, Sonino N, Guidi J. Understanding health attitudes and behavior. Am J Med. 2023;136(3):252–9. https://doi.org/10.1016/j.amjmed.2022.10.019
20 Fava GA. Patients as health producers: the psychosomatic foundation of lifestyle medicine. Psychother Psychosom. 2023;92(2):81–6. https://doi.org/10.1159/000529953
21 Sensky T. The person-centred clinical interview. Psychother Psychosom. 2024:1–7. (in press). https://doi.org/10.1159/000539055
22 Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatr. 2019;6(6):538–46. https://doi.org/10.1016/S2215-0366(19)30032-X
23 Di Mascio A, Shader RI. Behavioral toxicity of psychotropic drugs. I. Definition. II. Toxic effects on psychomotor functions. Conn Med. 1968;32(8):617–20.
24 Fava GA, Cosci F, Offidani E, Guidi J. Behavioral toxicity revisited: iatrogenic comorbidity in psychiatric evaluation and treatment. J Clin Psychopharmacol. 2016;36(6):550–3. https://doi.org/10.1097/JCP.0000000000000570
25 McEwen BS. Epigenetic interactions and the brain-body communication. Psychother Psychosom. 2017;86(1):1–4. https://doi.org/10.1159/000449150