FIRENZE Neuroscienze

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The Best Possible Cure

Learn Again, to Feel Good

The Aim of the Treatment in Psychiatry

It is not Medicine or Machines that Heal

Giornale dell'Istituto di Neuroscienze del Prof.Stefano Pallanti fondato nel 1989

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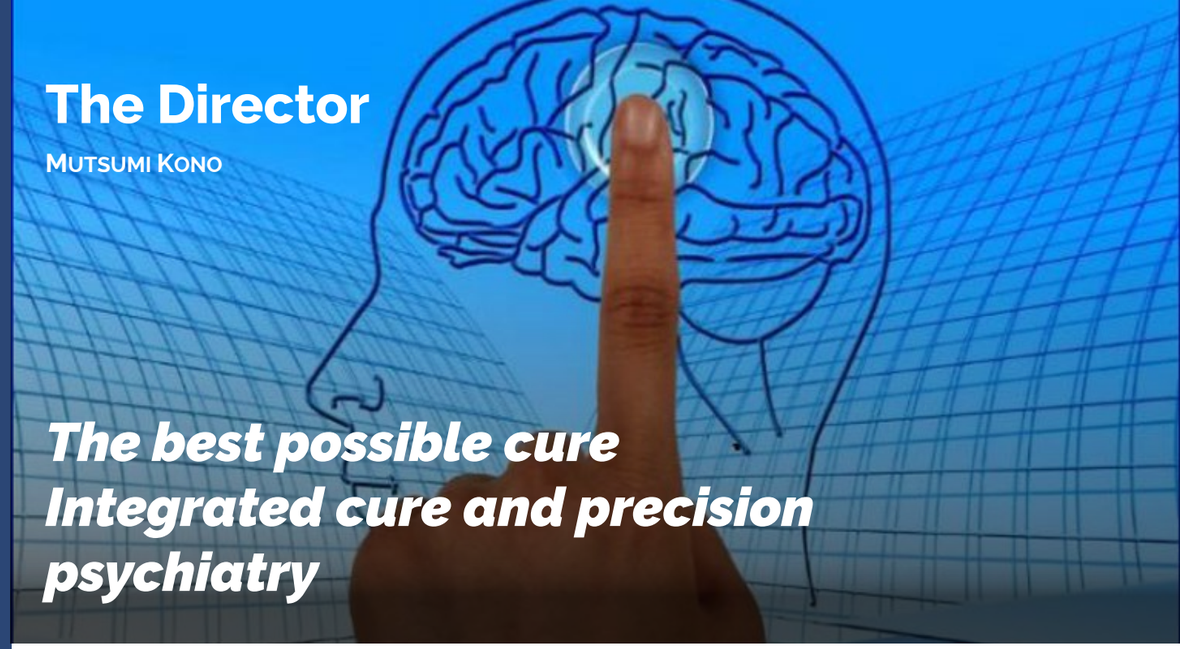


The Director

MUTSUMI KONO

The best possible cure Integrated cure and precision psychiatry

Recent research has brought about a significant shift in our understanding of psychiatric disorders. Today, we can consider these conditions as 'normal' medical illnesses, a concept that was previously not widely accepted.

This new concept, which is gaining traction in the field of psychiatry, shifts attention from symptom treatment to disease prevention, like the approach in other branches of medicine. It emphasizes the importance of early intervention and addressing the underlying causes of psychiatric disorders.

Furthermore, we can reach the criteria defining the recovery from psychiatric disorders by overcoming another of the widespread prejudices concerning psychiatry, the belief that one could only become ill but not recover. These criteria include not just the absence of symptoms but also the restoration of normal functioning and quality of life.

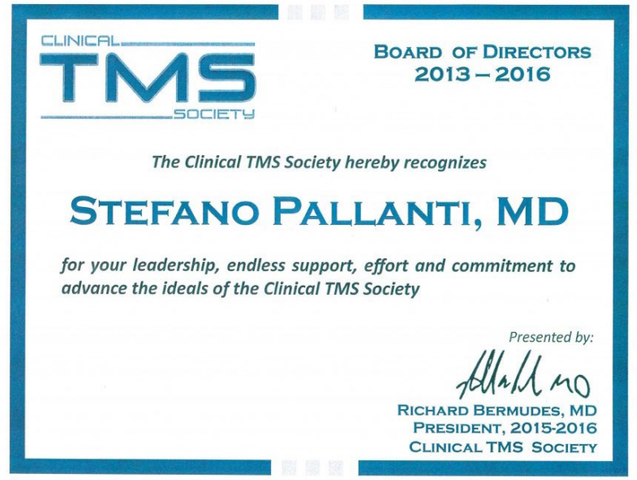
The definition of a disease is "a condition of the living animal or plant body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms." (2011. Scalable representations of diseases in biomedical ontologies. https://doi.org/10.1186/2041-1480-2-s2-s6).
In psychiatry, the main organ to treat is the brain. Still, the most recent discoveries oblige psychiatrists to consider the whole organism as the subject of treatment. Thus, they focus on the whole body, from the immune system to the intestines, cardio-circulatory system, and metabolism, and pay special attention to the individual's experience of his or her suffering.

Today, we know that many psychiatric diseases have a neurodevelopmental basis, already beginning during childhood but only showing up in later life. Research shows that disorders are related to dysfunctions of brain circuits, which start to be dysfunctional long before symptoms become clinically evident.
Unfortunately, we continue to use the term "mental," while the neurosciences urge us to go beyond this concept, which is misleading. For example, this stigmatization generates and

feeds another mistaken belief: "If disorders are mental, why should I undergo physical cures, for example, with medicines or diet or neuromodulation?"

Luckily, today's psychiatry offers a range of therapies, unlike almost any other medical specialization.
They all become useful considering the complex interaction between the brain, immunity, metabolism, and environment. Hence, Modulation therapies of cerebral activity (such as Transcranial Magnetic Stimulation) play a clearly defined role, together with other therapies that employ antioxidants and probiotics and combined with drugs that act on the central nervous system, while not excluding psychotherapies that encourage positive change. We also have neuropsychological rehabilitation interventions.

In TMS (Transcranial Magnetic Stimulation) with neuronavigation, the area of the cerebral cortex that needs stimulation can be precisely defined.
We can measure its functioning with Clinical Assessment Scales and with instrumental electroencephalography or neuroimaging* exams, by which new targets for treating these diseases can be defined. (*Neuroimaging: methods and tools to detect and reproduce brain activity in anatomical and functional terms).
Developing neuroscience studies allows us to delineate more precise diagnoses and treatment methods. Because the mechanisms of psychiatric illnesses are becoming clearer, cures are becoming more complex and integrated.
These resources are rarely exploited because of biases, despite the World Health Organization's emphasis on empowering the general population. Empowerment means being informed to monitor and track the whole cure process.
Overcoming the stigma associated with psychiatric disorders is not just a matter of funding and cultural awareness among doctors. It's also about changing preconceptions among the general population, both in terms of social stigma and personal inner stigma linked to individual history. It's a call for empathy and understanding.
For instance, ignorance concerning the functioning of the central nervous system, the presence of warning signs of disorders, and confusion of ideas about body and mind. A great psychoanalyst, Cesare Musatti, used to say that fear and ignorance always go hand in hand.
As Psychiatric disorders are not as respectable as physical illnesses, people acknowledge them only in highly acute circumstances. Today, psychiatry is often used only in the most acute phase of a disorder.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But we know that signs crop up long before symptoms do. For example, before a symptom of diabetes appears, there is already disturbed metabolism and a full range of other diabetes-related illnesses. Before a heart attack, the presence of hypercholesterolemia is already a warning signal.

In psychiatry, there are several predominantly subjective prodromal symptoms. The patient says, "I have difficulty doing this, I feel bad in these situations," etc., but he tends to see it as a personal failure or fault. There is a widespread prejudice that everyone is responsible for their mind.

So, psychiatric patients tend to see themselves as somehow responsible for their disorders, as not being able to control them because they are too weak.

If they are younger, they tend to see themselves as inadequate, or the guilt is pushed onto their family or, more generally, to their schooling. Family and education are essential in everyone's life, but no one is guilty of suffering. Ignorance about psychiatric illness also leads to a false attitude toward the disease itself. One fails to realize that psychiatric symptoms seriously impact the quality of life because they do not recognize it as a "real disease." After years of suffering, one thinks that recovery is possible with a single visit. But of course, this is not the case because the treatment of psychiatric disorders is many times a life-long process.

Many parents do not want a diagnosis and refuse treatment for their children because they fear that the "scarlet letter" may be stamped on themselves. They may turn to a psychiatrist only when their children are already an adult and when their disorders have become too complicated to stand and treat.

What we should fear is not disease but ignorance.
We must sweep aside all such prejudices so we can focus on using the therapeutic resources available, just as we would any other medical treatment.

Understanding that psychiatric disorders are actual illnesses has empowered us to take action. The first step was to overcome the stigma and initiate the cure. It's crucial to remember that it's not just the patient who benefits from early treatment, but our entire society.

The World Bank recommends that if governments want to invest in their future, they need to target more resources for treating psychiatric disorders, especially during childhood.

Epidemiology, that is, the study of the spread of psychiatric disorders, shows that in Europe, about a third of the entire population is affected each year by a psychiatric disorder (Wittchen et al., 2011).

For its costs, disability, and reduced productivity, as well as the significant reduction in life expectancy, the World Health Organization (WHO) rates depression as the most severe and disabling illness, more than cancer, stroke, and heart attack (S. Pallanti, Elementary Psychiatry, Carocci, 2016). WHO states that "there is no health without mental health" (WHO, 2005).

The Scientific Director

PROF. STEFANO PALLANTI

Learn, again, to feel good

At the heart of the feeling of being ill is the belief that one won't be able to change.

Those who are sick think that they will not be able to feel as well as before. They see no possibility of change.

The first step is when they start to have a positive doubt: "It could even be that **I will get back to live, to live my life**."

Depression is a disease but a very particular one in which you will not get well until you feel healed. And this experience occurs in different ways.

Sometimes, it is ephemeral: "Last night I felt well, normal," but then when I awoke, the same suffering returned.

At other times, there is a flash, a spark: "For a moment, the light came on again, and I was finally able to do what I had not even been able to think of doing for some time"; then, once again, the pall of depression.

At other times, it's a gradual clearing of the horizon, like an aurora. The world returns to life slowly, and the sounds, smells, and affections return. Time resumes its flow after it seems to stop. The affections had eclipsed behind the black sun of melancholy. Finally alive.

As I said, there is only healing if you get this experience of feeling good.

And this is not only because of what one subjectively feels. How we identify ourselves is central to our "mental well-being" concept.

Of course, we must only idealize this condition because feeling well doesn't generally correspond to feeling happy. Happiness is also an extraordinary condition that is not part of everyday life.

> *"*
>
> *It could even be that I will get back to live, to live my life.*

Perceiving the first signs of this positive change that restores you to life is also important because this renewed trust sets in motion the process of renewing your behavior.

Illness is always a limitation, a reduction.

At the cerebral level, it is also a limitation, a constraint, a reduction of freedom. You can't act, feel, or use your will when you suffer.

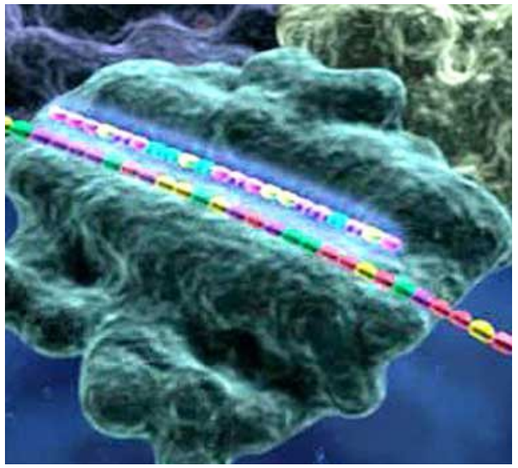
If we look at what happens in our brain, we find that the levels of those factors that guarantee its plasticity have been reduced; BDNF (the trophic factor that makes the brain grow) is reduced.

But when we begin to feel positive changes, it starts up again. Our neurons are reconnected and responsive to the experiences of life, which they physiologically absorb.
Regular connectivity resumes among the cerebral areas, which work like a well-rehearsed orchestra.

Whatever agent enabled my good functioning to resume, whether medicine, psychotherapy, magnetic stimulation, or something else, improvement will come if my frozen lake of suffering thaws.

I was in torment, now less so, and could not step out the door; I had no energy and now could move; I even shrank from sounds and now can listen to my favorite music.
The disease's constriction decreased, and the ballast and fear were reduced: with a little more confidence, "Now I can act, be the master of my life!"

This way, I am free from torment, thus allowing me to accomplish a fundamental passage.
Before, when they were ill, it was not possible, even if someone told them, "You have to exert your will." He was sorely mistaken. It is not a question of will because your will was always there: it is the vital momentum of a brain functioning at full throttle again.
And so, the subject, too, regains his place in the world.
Without this, there is no healing, without the



neurons resuming their plastic activity and the subject experiencing initial change and exposing themselves to new behaviors. We must learn to live again.

It is a new and useful concept that healing results from new learning, an active form of learning that the learner carries out by assuming behaviors that he couldn't before because of the debilitating effects of his illness.

What kept them from feeling good? The plasticity is no longer functioning. They could not do things, not consider themselves capable of doing things.

With improvement, everything starts up again, and here, perhaps intermittently, back there returns the confidence of being able to act and feel yourself in a new way.

Dr. Stefano Pallanti and Dr. Alvaro Pasqual-Leone. Dr. Pascual-Leone is a world-leading figure in the development of Transcranial Magnetic Stimulation (TMS) for its application in cognitive neuroscience, particularly in clinical applications in neurology, psychiatry, and neurorehabilitation.

What is the aim of the treatment in psychiatry?

The aim of the treatment in psychiatry means to improve the quality and lengthening of life, so it must be oriented towards healing and secondary prevention: the reduction of socially unacceptable behaviors or the disappearance of symptoms do not constitute "healing."

Moreover, with this approach the knowledge and techniques of psychiatry can be applied to the improvement of performance (sports, study, learning new subjects).

What are examples of inappropriate use of psychiatric care in which the goals of treatment have not been identified and shared?

1. Sedation, reduction of vigilance – never recommended

Recent studies have highlighted that the patient must try to maintain the best possible contact with his or her environment to develop the best collaboration and the most accurate monitoring of subjective conditions.

Still, my patients who come to the first visits often complain of feeling sedated.

This happens, unfortunately, because the treatments were prescribed at a time when the primary concern of the doctor was to mitigate the state of agitation of the patient. So, the doctor used drugs to achieve a sedative effect.

Sedation is never recommended, even when psychotic disorders present themselves: the goal should be the reduction of psychotic symptoms and not the reduction of vigilance or motor slowdown.

Furthermore, the sedation and motor slowdown (lethargy) should be considered as avoidable side effects!

The use of drugs deliberately directed to obtain these soporific, sedative effects belong to the past.

Even today, unfortunately, sleep treatment or narcotherapy, the so-called rapid tranquilization with sedation, continues to be practiced on psychiatric patients.

We know perfectly well that these practices have no scientific basis.

2. Untimely termination of treatment

Unfortunately, after the first improvement of the condition, many patients discontinue a therapy without agreeing to the ways and times with the professional who prescribed it.

That the old symptoms reappear - in a more severe form – often happens in these cases; or. new symptoms arise which are more difficult to treat: the dreaded relapse.

Behind every disorder there exists a vulnerability of the system that physicians may control or perhaps cancel only by maintaining adequate protection over time.

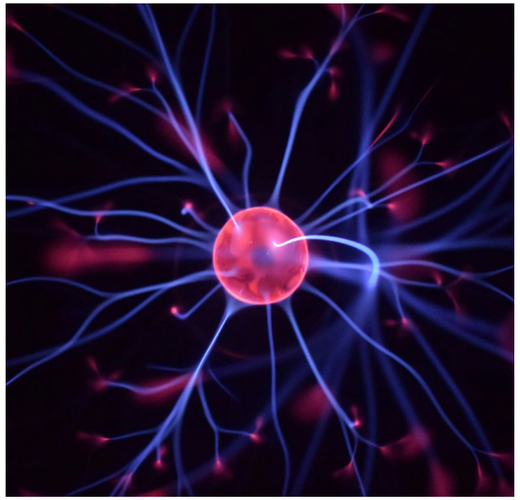
It would take much more time and effort to restore the dysfunction after relapse.

Healing

Treating oneself and overcoming the acute phase of the disease are the first goals to be achieved, but these effects are not sufficient to define a "cure."

Often the patient's request is to return to his healthy state, the way it was before the disease. The disease leaves a painful mark that many would like to erase.

But going back to the way it was before can



also mean reverting to the condition of previous fragility, the same state that led to the disorder.

Following the suggestions of the World Health Organization (WHO), the goal becomes more important, and the critical moment of the disorder must become an opportunity to know oneself, to learn more about the pitfalls of the disease, so as to commit oneself to changing one's vulnerable behavior.

It becomes essential to build, together with the doctor, a new awareness, a new style, a new balance that protects the individual as much as possible from relapse.

Healing as an objective. Is it possible?

Healing, for a large percentage of patients, posits a certain goal; thus, the WHO indicates healing as the real goal of treatment. The treatment should not only let one out of the acute phase of the emergency but start the patient again towards a new life.

How to achieve healing?

First, let us define "recovery": The American Psychiatric Association defines "recovery" this way:

"Healing from psychiatric disorders is a process of change through which individuals improve their health and well-being, live self-directed lives, and strive to reach their full potential."
Being cured, therefore, does not mean that one should no longer take medication or cease Psychotherapy or Neuromodulation Therapies. It is not merely a point of arrival, but a process of change aimed at improving the quality of life.

Many people feel confused about this "cure" aspect, and already in the acute phase of the disorder would like to aim, as a primary goal, to stop the treatment with drugs or to stop the therapies. In other cases, they may approach the specialist with the illusion that everything can be solved after a single medical visit.

The" single visit" scenario does not work because the disappearance of the symptom alone does not coincide with the disappearance of the disease.

Effective therapies rebalance the functioning of brain circuits that are malfunctioning; but, even after the remission of the symptom - even partial – the patient and consulting physician must continue for the necessary control and maintenance of what has been restored.

Why cannot we continue with the same therapy for a long time?

Under the surface of every disorder, moreover, there lies a vulnerability of the system that, only by maintaining adequate protection over time and regularly scheduling visits, re-evaluation sessions and booster treatment, can be controlled and even eliminated.

The brain exists as a plastic, adaptive organ: medicine, or Neuromodulation Therapies will allow it to make the best use of its plasticity: but for this to happen without symptoms' returning, therapy must be continued and balanced according to circumstances and environment over time.

This therapeutic protocol becomes even more relevant because each therapy, pharmacological or neuromodulation, can have a sequential adaptation, or have different objectives or even different diagnoses.

To give an example: the patient arrives in a severe state of depression, which immediately becomes the main objective of the beginning of the treatment. This is followed by the emergence of a background of anxiety disorders or obsessive preoccupations that led to the onset of depression, and the treatment is then adapted.

When the anxious and depressive symptoms will be eliminated, then problems of attention and concentration will emerge that have influenced a drop in self-esteem: here, again, the treatment will change its target and at the same time improve one's response to stress: Resilience.

This is also why individuals cannot continue with the same medicinal therapy for a long time without monitoring its effects.

What is the best defense against relapse?

Healing is not a grace that we derive from outside but a process of change - a new learning - in which you activate, with constancy, all the positive, personal resources of which you have become aware.

Healing demands a constant commitment, which becomes a new way of life, even while maintaining the necessary care: working for your well-being in a conscious way remains the best defense against the dreaded relapse, and it ensures the best road to recovery.

Prevention

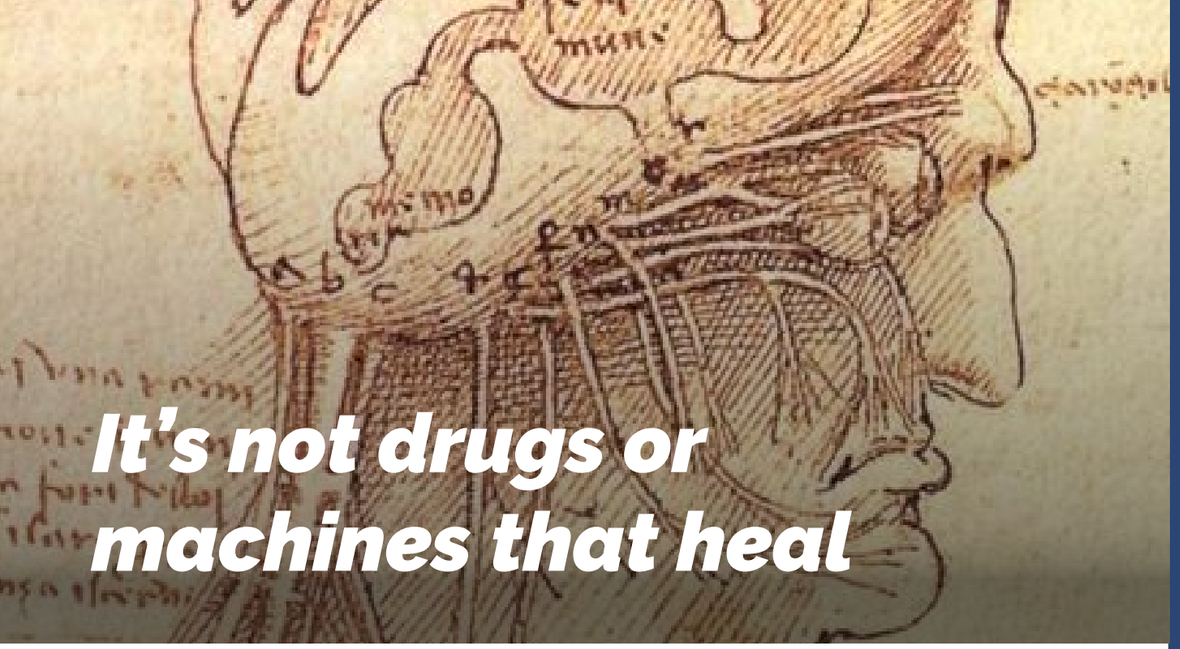
The evolution of science and medicine clearly demonstrates that it is possible to prevent relapses, the appearance of a psychiatric disorder, and the worsening of diseases.

What can be prevented:

- Violence, including domestic violence
- Risk behaviors
- Improper eating behaviors
- Addictions to substances, internet, gambling, and pornography
- Psychosis
- Worsening of neurodegenerative diseases (such as Parkinson's, Alzheimer's and Huntington's disease)
- Anxiety disorders, post-traumatic stress disorder (PTSD)
- Loneliness: statistically correlated with most psychiatric disorders because the brain circuits that elaborate social processes correlate with the immune response. Therefore, psychological science should address behavioral health.

Psychiatry is a science that concerns itself with all of us because it addresses behavioral health and not just individual disorders.

To make prevention programs widespread and affordable, today's society must give new attention to psychiatry and overcome any self-fulfilling fatalism or social stigma.



It's not drugs or machines that heal

A widespread belief among doctors and health professionals is that drugs, especially the "new drug" or the most recent technological tool, heal diseases.

It is not valid.

Many patients, disillusioned after seeking solutions from various local and international psychiatrists, turn to Prof. Stefano Pallanti. His unique approach to personalized treatment, which has led to significant improvements for many patients with highly resistant disorders, is a beacon of hope in psychiatry.

To their surprise, many patients realize that they have been cured with medicine that they have already used without success. Probably the same drug was dosed or combined differently: variations that are not flashy but which, so to speak, "make a big difference."

Ultimately, it's not the drugs or the machines that make **the difference but the doctor's pivotal role in selecting, calibrating, and guiding the treatment path in collaboration with the patient.**

This human element is the true essence of effective psychiatric care.

The essence of precision psychiatry lies in crafting a treatment plan exclusively **for each individual, acknowledging their unique characteristics and needs.**

We must always start with the Diagnosis, but how many of the patients we see, despite having been treated or even hospitalized, have NEVER received a written classification and Diagnosis?

The Diagnosis must be the starting point. It can be modified, subtyped, or specified, and if new aspects emerge during treatment, expanded to include them.

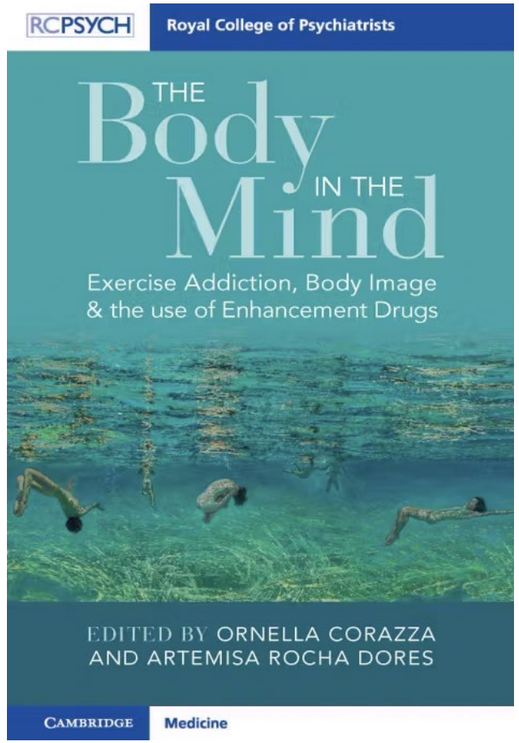
Then there is the story of each person: the history of the family, the history of the external and biological events that have impacted the trajectory of the disorder, and above all, the PERSON.

Everyone has physical, medical, immunological, relational, familial, and genetic characteristics that distinguish them from others. Other factors are age, gender, family status, and treatment predisposition. Then, there are relational and communication styles and individual expectations. For this reason, the doctor must consider and clarify the therapeutic goal and share it with the patient.

Treatments only work when all these factors are considered and shared by patients: Personalization.

Drugs

There is no one-to-one correspondence between the symptom and the cause. Therefore, **there is no one-to-one correspondence between the symptom and a drug.** Unfortunately, there is still no culture of these aspects. **The same symptom, as reported by the patient, can express different mechanisms at the origin, i.e., various diseases.** For example,



under the umbrella of "Depression," there are at least five subspecies, each of which has a different cause – the malfunctioning brain circuitry.

To simplify, reduced tolerance to stress, reduced energy, reduced perception of gratification, increased negative feelings, worsening of cognitive functions, and many other manifestations or combinations can determine a clinical picture generically defined as "Depression."

We can describe all psychiatric and medical symptoms in the same way. Today, however, **we distinguish between drugs for treating symptoms and treatments that modify and reduce vulnerability to disease.**

At this point, we have understood that the doctor's ability to choose the drug that acts on the particular brain circuit concerned is crucial; the symptoms are used to orient oneself but must be 'translated and interpreted.' Today, this approach to the clinic is called '**Translational**.'

To do this, the doctor must possess notions that are broadened daily and acquired through clinical research. He must also know the results of research in primary medicine.

The informed clinician is also necessarily a researcher.

It will take about 17 years for the pharmaceutical administrative agencies to include a scientific data document, such as the effectiveness of a new treatment, in their guidelines.

For this reason, it happens that some patients have to take 'off-label' drugs. Off-label means that their symptoms or Diagnosis are not among those already approved and indicated in the package leaflet of the chosen drug. This practice, while sometimes necessary, highlights the challenges in psychiatric treatment

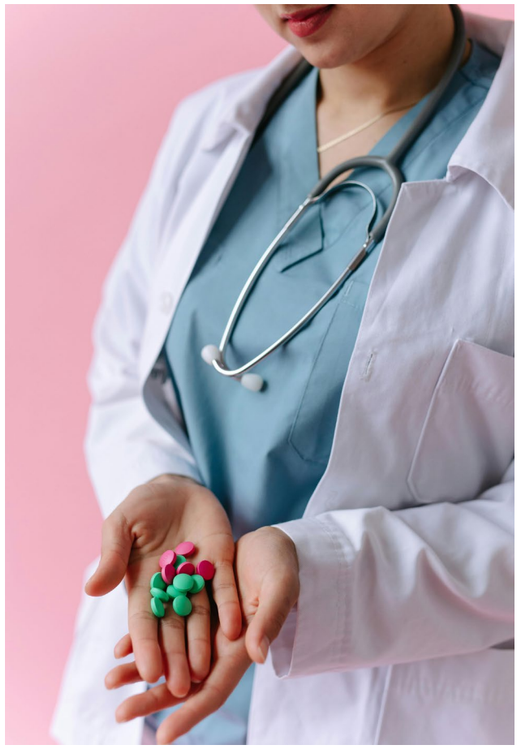
and the need for personalized approaches.

Drugs for the treatment of depression are often combined today, but this does not have to happen simply by matching the sum of the symptoms with the sum of the drugs. Particularly in older people, interactions and side effects become incalculable, and it is necessary to withdraw drugs rather than increase them.

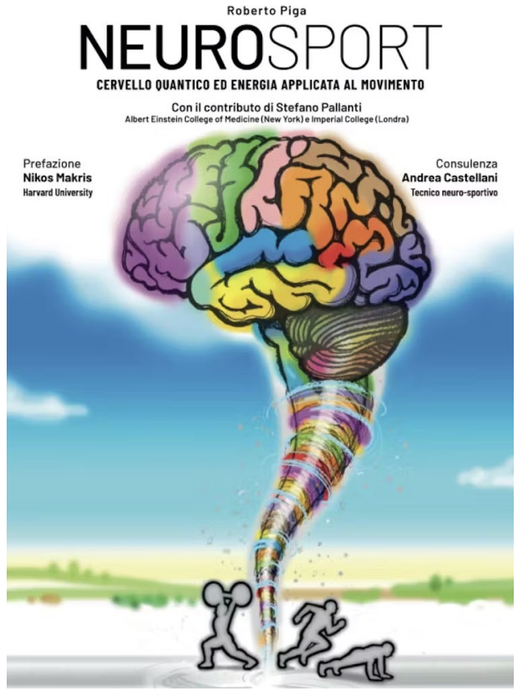
It is necessary to remember that **the purpose of treatment is to improve and extend life, not just to eliminate** the symptoms of a disease; the two objectives cannot always coincide.

After the right drug choice, it is essential to individualize the achievement of the minimum **therapeutic dose**, which is different for each person. We know of the significant variability in the metabolism of the same drug. Since it is not always possible to perform a dosage of the drug's absorption levels in the blood, doctors can find the "really right treatment" only by paying attention to what the patient reports. Each person can respond in a particular way to each drug.
While the institutional leviathan of standardized guidelines and treatments still blocks the health care system, modern medicine, and psychiatry propose a personalized approach beyond guidelines called off-label treatments. Dr. Pallanti usually performs off-label treatments in the day center's care framework after providing all helpful information on the new medicine's effects so that patients are not left alone to experience its effects.
Dr. Pallanti personalizes the treatment using a method based on his experiences. This approach aims to correct the disorder without harming other bodily functions. The dosage is crucial because, in some cases, the same drug can have different effects at different dosages. Nowadays, these drugs are considered 'multifunctional.

The same molecule becomes three different "drugs" in various doses.



It is a measured art.
The last consideration is for the duration of the cure. Why should one continue to take medication or follow up treatment with machines if the condition has improved? Why do you have to have a check-up very frequently if the treatment is working?
Today, we understand that body system vulnerability causes every disruption, which we can manage and even eliminate by maintaining consistent protection over time.
The time it takes for therapeutic effects to become apparent varies from person to person. Patients see improvements after a few weeks, but sometimes it may take months. Effective therapies alter the malfunctioning brain circuits, so they require adaptation. Even after therapeutic effects appear, patients should continue with the treatment.
The brain is a plastic organ, and medicine will allow it to adapt in the best possible way and use its plasticity well. However, for this to happen without recurring symptoms, it will be necessary to continue and balance the dosage according to the circumstances and the environment.
In this way, we can avoid or at least minimize the risk and severity of relapses.
Machines – a technological tool
Certainly! Here's the revised text:
In our situation, we are discussing Neuromodulation machines such as TMS (Transcranial Magnetic Stimulation), tDCS (Transcranial Direct Current Stimulation), PBM (Transcranial Photo-Bio-Modulation), and Light Therapy.
Similar to medications, different protocols, target areas, and methods are available for each affected brain circuit. There is no direct match between a symptom and the protocol.
If we follow the "Standard" approach instead of customizing the treatment, as is feasible today with Neuromodulation, these treatments may not reach their full potential.
The Course of Treatment
Each therapy, pharmacological or neuromodulation, may have a sequential adaptation that requires different objectives or treatments



for other diagnoses.

To give an example: the patient arrives in a severe state of anxiety, which is, therefore, the primary objective of the beginning of the treatment, then a background of depression and mood disorder emerge that have facilitated anxiety: the treatment is modified. Finally, when the anxious and depressive symptoms are gone, perhaps problems with attention and concentration will emerge: again, the treatment may change the target.
The best treatment always arises from the personal relationship between a doctor and his patient or somewhat between a patient and his doctor. With the doctor listening to the patient, drugs and machines work.

Transcultural Observations of Obsessive-Compulsive Disorder

"One must observe the proper rites."

"What is a rite?" asked the little prince.

"Those also are actions too often neglected," said the fox. "They are what make one day different from other days, one hour from other hours."

—*The Little Prince*, by Antoine de Saint-Exupéry

Obsessive-compulsive disorder is a common and serious illness whose core symptoms seem to merge more closely with normal human behavior and cultural traditions than those of most other mental illnesses (1).

Obsessions are recurrent and persistent thoughts, impulses, images, or doubts that are intrusive or inappropriate and that cause anxiety or distress. Since the persistent thoughts are often morally or physically repugnant, they can cause great shame. For this reason, many sufferers do not reveal their struggles. Even when sufferers recognize their worries as a product of their mind, they interpret it as a failure to master their own mind. Usually those suffering from the disorder try to ignore or suppress their obsessions or neutralize them with other compulsive thoughts or actions. Compulsions are repetitive behaviors, including mental acts, that a person feels driven to perform, either in response to an obsession or cued by some concrete object according to rigid rules. In the past, obsessions and compulsions were viewed as disparate elements, but recently the two have begun to be integrated into a one-dimensional approach. Principal-component analysis identifies five factors explaining 65.5% of variance in outcome: symmetry/ordering, hoarding, contamination/cleaning, aggressive/checking, and sexual/religious obsessions (2). These factors also have high familiality in sibling pairs with obsessive-compulsive disorder, which suggests that they could be genetically determined traits (2).

"Results suggest that obsessive-compulsive disorder is more deeply embedded in common neurobiology than in cultural differences."

Obsessive-compulsive experiences and symptoms have been reported in 90% of healthy adults, particularly during childhood, when it would seem that these symptoms facilitate many types of learning (3). When it is not dysfunctional, obsessionality may be socially rewarding. For example, 50% of reported cases of female adult-onset obsessive-compulsive disorder begin in the postpartum period (4). Accordingly, obsessive-compulsive disorder has been described as a pathological form of altruism or maternal love, perhaps a result of the deregulation of the brain circuits responsible for threat detection as part of normal parental behavior (5). Obsessive-compulsive traits are also manifested as "magical thinking," a common mental technique for asserting control over the world through rituals. Magical thinking, an ancestor of science in most cultures, cognitively represents the concept of thought-action fusion. One of the roles of magical thinking is the formation of fear of and responsibility for causing harm to others (6).

The epidemiology of obsessive-compulsive disorder is quite consistent in different countries and across cultural studies. Results from 15 clinical samples from different continents suggest that cultural variation has minimal influence on lifetime prevalence rates, which range from 1.9% in Korea to 2.5% in Puerto Rico (7). As might be expected, symptoms often take on characteristics of the patient's culture. For example, a correlation between compulsive ablution, poor insight, and religious rituals has been reported among Egyptian Muslims (8). The religious connotation of obsessive-compulsive disorder in Muslim culture is denoted by the term *weswas*, which refers to the devil as well as obsession. The early Christian definition of the term "obsession" has the same connotation, meaning partially lucid diabolic possession.

Matsunaga and colleagues report in this issue of the *Journal* the first comprehensive analysis of the symptoms of obsessive-compulsive disorder in an Asian population. Due to its history of isolation, the Japanese population is one of the largest populations with a single ethnicity. Some of Japan's isolation is reflected in its unique cultural institutions, which rely on highly ritualized ceremonies to regulate aggression in social interactions. It has been said that the Japanese have made courtesy a religion, as concern regarding negative social evaluation is much stronger in Japan than in Western cultures (9). Shame has been linked to suicidal behavior and even glorified in Japanese literature by Yukio Mishima (10) and others. Despite these well-known cultural differences, the symptoms of obsessive-compulsive disorder in Japan are remarkably similar to those in other cultures. Four factors explain 58% of the variance: contamination/washing, hoarding, symmetry/repeating and ordering, and aggressive/checking. Symmetry is associated with an earlier age of onset and, along with hoarding, accounts for decreased function and poorer outcome from treatment. The results suggest that obsessive-compulsive disorder is more deeply embedded in common neurobiology than in cultural differences.

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Dr. Pallanti reports no competing interests.

Why doesn't my treatment work?

Many patients come to **Dr. Pallanti** after having visited many doctors in Italy or in their own countries, and many times they went to visit doctors in other countries around the world. Patients often come to the USA but even as far away as Australia, in search of treatments that work for them. Many patients claim they feel worse after visiting multiple neurologists and psychiatrists.

The reasons for not responding to treatment include:

- You have been misdiagnosed or partially diagnosed.
- The diagnosis may be correct, but you are not responding to therapies, due to peculiarities of drug metabolism that have not been individually considered.
- Inappropriate treatment developed a resistance to treatment.
- There exist disorders for which there are not yet guidelines; therefore, it may be necessary to undertake "off-label" treatments. Prescribing such treatments requires the doctor to go beyond the standard guidelines and protocols and refer to the latest scientific research.
- Coexisting psychiatric and neurological disorders were treated separately, and the treatments interfered with each other (e.g., Tics and cognitive disorders, Bechet and psychiatric disorders)
- There still exist unknown diseases

Having the correct diagnosis provides the first step in formulating a personalized treatment. There are no treatments or medicines that suit everyone.

What commonly happens with an Incorrect or Incomplete Diagnosis:

Almost all patients who come to Dr. Pallanti arrive with incorrect or incomplete diagnoses.

ADHD, for example, does constitute an important comorbidity of some psychiatric disorders but is commonly ignored. If the ADHD is not treated in Depression, Anxiety, Obsessive-Compulsive Disorder or Parkinson's, no significant improvement results.

The Consequences of Wrong Choice of Medication:

We often see patients taking antidepressants (unsuccessfully) because they felt "depressed," and the doctor then prescribed antidepressants.

The same symptom, as reported by the patient, may be an expression of different mechanisms at its origin, that is, of different disorder.

For example, under the umbrella of "Depression," there are at least five subspecies, and each of them has a different cause, the brain circuit's malfunctioning.

So, each subspecies has to be treated with different drugs or strategies.

There is no one-to-one correspondence between the symptom and the cause. So, too, there is no one-to-one correspondence between the symptom and a drug. There is no culture of these aspects, yet.

Unfortunately, doctors prescribe drugs using standardized, guideline criteria without investigating which brain circuit actually is involved.

The Consequences of Wrong Dose Prescription:

A doctor prescribes a patient a low-dose serotonergic antidepressant because he does not know its proper usage. It fails to work; and after two months. the patient goes back to the doctor. The doctor changes the medicine and gives another serotonergic at a minimal dose. It, too, does not work, and the third time the patient returns, the doctor administers another serotonergic again at a minimal dose.

The patient consults another doctor, but always a minimum dose serotonergic is prescribed, and the clinical picture does not change.

The treatments did not work because they did not reach the minimum therapeutic dose.

Among other factors, physicians cannot jump from one medicine to another because there

"My priority requires that I listen to what the patient says and how the patient tells his story, whence I translate the discourse to unveil the dynamics of distress in relation to the patient's biography and brain functioning, evidenced by objective evaluations."

"I cherish ethical principles first, and I commit to care for each person as a whole, respecting his or her dignity in each phase of life."

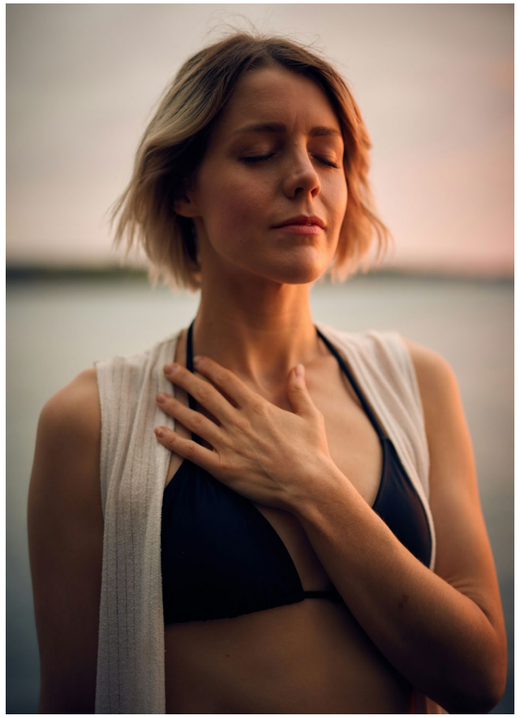
Dr. Stefano Pallanti

are interactions, and especially intersections in the mechanisms of action that cannot be disregarded.

The patient continues on with the same therapy that does not work; and, in the meantime, he becomes resistant. Thus, it becomes more difficult for him to respond to treatment because the longer he is sick, the more difficult it becomes to treat him. Such a progression commonly occurs in Italy and abroad.

The Consequences when the doctor does not Prescribe the Most Effective, New Drugs:

Patients can now find out about new drugs on the Internet, but their doctors do not prescribe them because they do not know them or how to use them. Often, those who do not know the new drugs disqualify them. If a physician prescribes them, he does so at a minimal dose, and therefore they do not work.



Personalized care for greater success:

The treatments should be **personalized**: each person should receive a treatment designed specifically for him or her.

The starting point lies always in the diagnosis: it can be under-typed or specified; and, if new aspects emerge during treatment, expanded to include other conditions that require treatment.

Then we must consider the story of each, individual person: the story of the family, the story of the external and biological events that exerted an impact on the trajectory of the disorder, and most importantly, the person.

Everyone has physical, medical, immunological, relational, familial, and genetic characteristics that distinguish him or her from everyone else. There are other factors to consider: age, gender, family status, and predisposition for particular treatments. Then, we must consider the relational and communication style, the individual expectations.

For these contributing aspects, the doctor must consider and clarify the therapeutic objective, which must be shared with the patient. A treatment works when all these factors receive appropriate attention, shared between the doctor and the patient. This holistic approach defines the "personalization of care."

How to use medicine

There is no one-to-one correspondence between the symptom and the cause.
Thus, there is no one-to-one correspondence between any symptom and specific medication.

With the recent development of clinical psychiatry, physicians may distinguish between medications that treat symptoms and medications that modify and reduce vulnerability to disease.

So, the doctor must choose the medicine that acts on that brain circuit affected: the symptoms serve to orient a medical context, but they must be translated and interpreted: today this type of approach to the clinic is called "translational."

"It takes hospitals and clinics about 17 years to adopt a practice or treatment after the first systematic evidence shows it helps patients" (Harvard Business Review https://hbr.org/2019/08/4-ways-to-make-evidence-based-practice-the-norm-in-health-care).

The delay in evidence-to-practice causes some patients to take off-label medicines: it means that their symptoms or diagnosis are not among those already approved and indicated in the information sheet of the chosen medicine.

Physicians often combine medications for the treatment of depression, but this should not be done by simply matching the sum of symptoms to the sum of medications. Particularly in the elderly, the interactions and side effects become incalculable, and it becomes necessary to reduce medications rather than to increase them.

We must all remember that the goal of treatment means to improve and lengthen life, and not merely to aim at the symptoms reduction. The two goals do not always coincide.

Minimum Therapeutic Dose

After the choice of the right medicines, it is

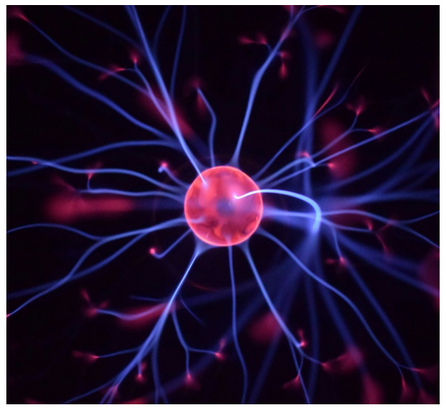
important to individualize the achievement of the **minimum therapeutic dose**, which will be defined specifically for each person. The guidelines, on this aspect, do not report valid data for every subject.

We know that there exist countless variables that determine the metabolic change from the absorption of a particular medicine: without the ability to administer a consistent dosage of any medicine's absorption levels into the blood, we can only attend to what the patient tells us, as the guide to identify the right treatment.

Each person responds in a specific way to each medication.

If the medicine does not reach the minimum therapeutic dose, it fails to work; and, it could make the person intolerant to that medicine, which implies the person will no longer be able to take it, even if it turned out to be the right one with a different dosage.

Modern medicine and psychiatry propose a personalized approach beyond strict guidelines and standardized treatments.



Therefore, in addition to providing any useful information on the effects of new medicines, whenever possible, Dr. Pallanti prefers that the patient not be left alone to experience the effects of a treatment, but that any effects take place in the controlled environment (Day Center).

Dr. Pallanti tries, with a method validated by his experience, to arrive at the personalization of the treatment that achieves the minimum sufficient to correct the disorder and no more.

The dosage proves fundamental because in some cases a different dose of the same medicine corresponds to different functioning: today, in fact, these medicines are defined as "multifunctional."

In these cases, we could say that we physicians face different medicines in the same molecule, if employed, using different dosages. Such differentiations define an art, measured.

Frequently, patients with psychiatric disorders have multiple comorbidities: for example, those with compulsive behaviors such as Trichotillomania may also have anxiety, depression, sleep disturbance, and more. These disorders often persist for a long time.

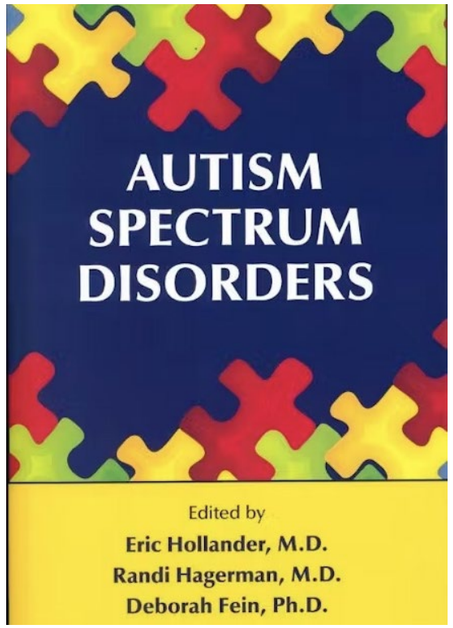
We cannot treat everything in one solution, so we should proceed in stages: a procedure should establish priorities and a hierarchy of goals.

Normally, the first target is the one related to the most disabling disorder: having improved that one, we go on treating other aspects.

Sequential adaptation of therapies

Each therapy, whether involving pharmacology or neuromodulation, may have a sequential adaptation or have different objectives; it may be designed for different diagnoses.

To give an example: the patient arrives in a severe state of anxiety - which becomes the primary objective at the beginning of the treatment - then a background of mood depression emerges that has facilitated the anxiety.



We modify the treatment; and finally, when we have eliminated the anxiety and depressive symptoms, perhaps problems with attention and concentration may emerge. Again, the treatment will have to change target.

Duration of Treatment

Once the condition has improved, why do we have to continue taking the medications or perform the follow-up, neuromodulation treatments?

Why must we do the checkup visits very frequently if the treatment works?

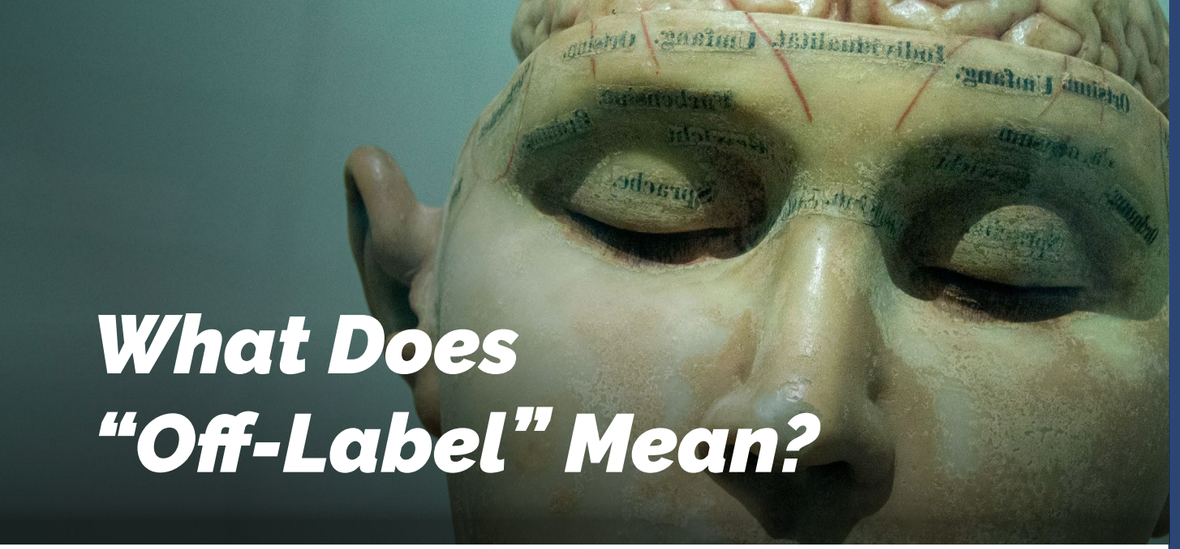
Because we know that behind every disorder there lurks a vulnerability in the system that only by maintaining adequate protection over time, can be controlled, and even canceled.

The appearance of therapeutic effects varies from person to person: in some cases, we might observe an improvement after a few days, but sometimes, it can take months.

Effective therapies modify the functioning of brain circuits, thus improving the condition; but even after the appearance of therapeutic effects, it remains necessary to maintain what has been restored.

The brain exists as a "plastic," adaptive organ, and the medicine and the neuromodulation will allow it to adapt in the best possible way, to use its plasticity well: but for these salutary modifications to happen without the symptoms' recurring, it will be necessary to continue and to balance the dosage according to the circumstances and the environment.

When we follow our own protocols, it will be possible to avoid or at least minimize the risk and severity of relapses because in that case it would take much more time and effort to correct the dysfunction.



What Does "Off-Label" Mean?

"Off-label" indicates the use of a drug or medical device for a protocol not officially included in the guidelines and not described on the instruction sheet.

"It takes hospitals and clinics about 17 years to adopt a practice or treatment after the first systematic evidence shows it helps patients" **(Harvard Business Review).**

During this long period of time, scientific research produces new advances daily: consequently, a large gap develops between approved treatments and those not yet approved but scientifically tested and proven to be effective.

Only a doctor who acquires knowledge of advanced clinical research daily can prescribe off-label treatments, whether pharmacological or via medical devices. Those who limit the use of medicine within the 17-year-old guideline and do not explain how more can be done by scientific evidence lack updating.

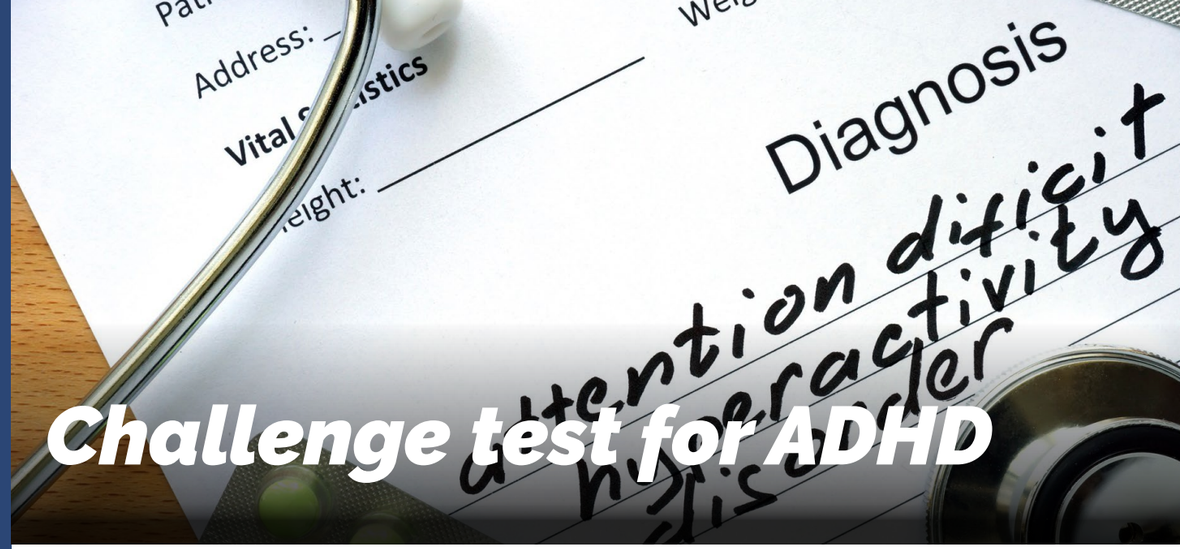
The FDA, when deciding to approve a product or drug, must consider whether the benefits outweigh the risks. The FDA usually tends to approve a product that has some calculated risk if the potential benefit is significant, such as an artificial heart valve that can save someone's life.

The process for approving medical devices such as Transcranial Magnetic Stimulation (TMS), Transcranial Direct Current Stimulation (tDCS), or Photo-Bio-Modulation - therapies that do not present obvious risks - typically proves very lengthy.

In addition, the FDA, to determine whether the product, drug, or food additive performs as safely and effectively as it claims to be, does not conduct its own testing but instead reviews the results of independent clinical and laboratory testing. Therefore, just because a device has been approved by the FDA does not always mean that it represents the best solution currently.

The FDA approved Transcranial Magnetic Stimulation (TMS) for Resistant Depression in 2008 and for Obsessive-Compulsive Disorder in 2018. This means that TMS for other disorders, and other neuromodulation methods remain off-label, for now.

We certainly know, however, that the indications for neuromodulation therapies have been scientifically proven and established.



Challenge test for ADHD

Background and considerations for the use of medication:

A widespread (mistaken) belief is that the medications used for ADHD are stimulants.

It is the opposite.

Those who take them for the first time are surprised that the most immediate effect is unusual calmness and lucidity. These effects are a sign that we are on the right track, and it is important to document them because they give the doctor a guideline and encourage him to proceed more swiftly in that direction.

The second prejudice is that "one becomes addicted".

But addicted to what?

Instead, it is the disorder, in this case, ADHD, that affects the life of the individual suffering from it. It does not allow them to focus on what they would like to do or to have the necessary steadiness in situations where needed. One does not depend on a drug, but it is indeed the disorder that conditions one's entire existence: it does not allow the individual to make choices freely. The use of medication is not about addiction but about managing the symptoms of the disorder to lead a more functional life.

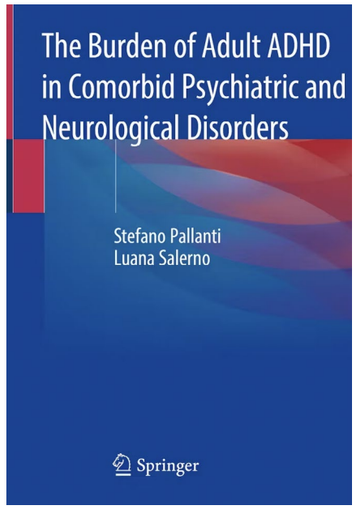
In the case of ADHD, one must choose between being 'addicted' to the disabling conditions of the disorder and suffering from them and leading an acceptable life both subjectively and objectively by taking medication.

It's important to remember that the choice to manage ADHD is a personal one, and it's a decision that can bring a sense of empowerment.

How does the Challenge Test work?

Some medications require initial administration in a controlled environment (Day Centre) to observe the immediate reactions and assess their effectiveness or the appearance of possible side effects. Among the medications requiring such protocol are those indicated for Attention Deficit Hyperactivity Disorder (ADHD).

Methylphenidate is the most widely used psychostimulant for the treatment of ADHD in both childhood and adulthood (Spencer et al., 1996; Santosh & Taylor, 2000; Nice, 2008).



This medication begins to show clinical activity approximately thirty minutes after oral administration. It reaches its peak plasma concentration and activity after one hour, and its therapeutic effect lasts approximately three to five hours. After taking the medication, responses to tests of attention, vigilance, visual and verbal learning, and short-term memory are improved (O'Toule et al., 1993).

The side effects of psychostimulants, particularly methylphenidate, are generally modest and easily manageable (Spencer et al., 1996; Elia et al., 1998; Santosh & Taylor, 2000). The most common effects are appetite loss, insomnia, and upset stomach: one can prevent insomnia by avoiding evening dosing and prevent lack of appetite and gastrointestinal issues by taking the medication after meals. When taken correctly, weight loss, headache, and abdominal pain are rare and temporary and rarely require modification or discontinuation of therapy (Barkley et al., 1990; Santosh & Taylor, 2000; AACAP, 2002).

Before prescribing psychostimulants, the doctor will prescribe routine blood tests and an electrocardiogram.

To assess the medication's effects on inattention and impulsiveness, a battery of tests is administered before and after the medication is given, during its effects (challenge). In addition, the drug's tolerability is monitored through repeated measuring of blood pressure and heart rate. Medical assessments are combined with the results of neuropsychological tests to adjust the dosage. This process of adjusting the dosage is called 'titration ', which is done to find the right balance between symptom management and potential side effects.

The administration protocol described above requires the patient to be present in person at the Day Centre for at least one day. In this way, we can carry out all the pre- and post-challenge assessments and allow the doctor to manage the development of any side effects.

Subsequently, periodic clinical check-ups will be necessary to adjust the drug's dosage (titration) and assess its long-term therapeutic effects and any undesirable side effects.
After an initial period of treatment with short-release methylphenidate, the doctor may decide to replace it with the extended-release (or modified-release) version, which guarantees good efficacy and coverage of ADHD symptoms for most of the day.

Doctors can treat stimulants only when the patient has a correct diagnosis supported by the results obtained from clinical and neuropsychological instruments. Without this, the assessment protocol to obtain diagnostic certification will be necessary, leading to a Challenge Test and subscription.

Importance of the precise diagnosis and the specific treatment

Most of the patients who come to Dr. Stefano Pallanti have already undergone treatments without resolving the problem, which has often proven resistant to treatment.

They arrive with partial diagnoses or even without a true diagnosis. They report experiences in which they directly go under the prescribed treatment after the interview with doctors without thorough, psychometric or neurofunctional evaluations. Very often physicians prescribe treatments that lack a structured diagnosis.

Symptoms are not the diagnosis in themselves, and the goals of treatment must be shared and directed at the causes of the disorder. Therefore, having a precise diagnosis provides the first step towards success.
Psychiatry requires moving from studying traditionally classified diagnoses to understanding the constructs and mechanisms involving certain brain circuits specifically defined for each maladaptive behavior (Cuthbert & Insel, 2013; Insel et al., 2010).

The same symptom, as reported by the patient, could be the expression of different mechanisms.
For example, the symptom of Depressed Mood takes on different meanings in the context of ADHD, Autism, Anxiety, Obsessive Compulsive Disorder, Substance Disorder, Somatic Pain Disorder, Fibromyalgia, PANDAS, Parkinson's, Schizophrenia, and other conditions.
Furthermore, the care must be centered on the person, his or her, individual biological characteristics but also the person's individual life history.

The diagnosis must be the starting point; it can be modified, subtyped, or specified. If new aspects emerge in the course of treatment, that course of treatment can be extended to include other conditions that require attention.

Then, the physician must consider the history of each person: the history of the family, the history and context of external and biological events that impacted the trajectory of the disorder, and above all, the person.

Everyone has physical, medical, immunological, relational, familial, and genetic characteristics that distinguish him from anyone else. There exist other factors to consider: age, gender, family status, and any predisposition to particular treatments. Then, there are relational and communication styles, and individual expectations: for this reason, the doctor must consider and clarify the therapeutic goal, which the physician must share with the patient.
Treatments only work when physicians consider all these factors and share their findings with patients. Such cooperation defines the "personalization" of medical treatment.
How can we achieve a precise Diagnosis?
Throughout medicine, different and progressive levels of specialist care receive definitions, but in psychiatry, these concepts still find little application.

Symptoms are not in themselves the diagnosis, and the goals of treatment must be shared and directed at the causes of the disorder.

Therefore, the "personalized diagnosis" provides the first step of this evolution defined for each maladaptive behavior (Cuthbert & Insel, 2013; Insel et al., 2010).
Psychiatry requires moving from studying traditionally classified diagnoses to understanding the constructs and mechanisms involving certain brain circuits specifically
In fact, in addition to the clinical definition of any disorder, physicians must necessarily define its specifics, the characteristics of the development of the disorder, and the neuro-functional correlates, with particular attention to cognitive functioning and the inflammatory response.
All these factors cannot be accounted for in the interview alone but require the use of psychometric tools which can be followed by functional assessments.
This first step takes us from General Psychiatry to Specialist Psychiatry, or the second level, and then to the Neuroscientific, or the third level.

PRECISION DIAGNOSIS IS DEFINED THROUGH LEVEL II AND III TOOLS.
The Institute of Neuroscience offers precision diagnosis through level II and III tools.

I Level - General Psychiatry

- Clinical interview

II Level - Specialized Psychiatry

- Subtype diagnosis
- Definition of specifiers
- An objective gravity measurement
- Attribution of a degree of resistance
- Evaluation of comorbidities
- Psychodiagnostic evaluations
- Psychometric assessments
- Neurofunctional evaluations
- Assessments of cognitive functions
- Rating scale for the quantification of symptoms
- Multidisciplinary evaluation with an Immunologist, Neurologist, Rheumatologist and other specialists, depending on the case.

III Level - Neuroscientific Psychiatry

- Metabolic and immunological evaluations
- Inflammation ratings
- Gut-screening
- EEG
- ECG
- P300
- PET
- MRI
- blood tests
- Plasma level tests
- Genetic tests for pharmacological response
- Challenge test for verifying the tolerability of medicine.

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