Psychotherapy and psychiatric drugs in psychiatry: what relationship, and what hierarchy?

Psicoterapia e psicofarmaci in psichiatria: quale rapporto e quale gerarchia?

In the second half of the last century, many clinicians-mostly psychoanalytically oriented-have opposed the use of psychoactive drugs for the treatment of mental illness, particularly in the course of psychotherapy, arguing that they suppress conflicts and states of mind considered essential for the understanding of suffering. Furthermore, psychoactive drugs were supposed to have a negative influence on psychotherapy by making it less effective [1]. In reality, in 1974 research demonstrated that integrated therapy (i.e. combined use of medication and psychotherapy) is not harmful to the patient, but is actually useful [2]. However, the conflict between pharmacotherapy and psychotherapy had already made a great disservice to patients, sometimes delaying the required drug treatment (e.g. the importance of duration of untreated psychosis [DUP]for the prognosis of schizophrenia) or other avoiding effective psychological interventions that could lead to a better quality of life and reduce the risk of suicide. This may be the case when considering dialectical behaviour therapy (DBT) [3] or exposure and response prevention (ERP) techniques in cognitive behavioural therapy (CBT) for borderline personality disorder (BPD) and obsessive compulsive disorder (OCD) [4], respectively.

Unfortunately, today, despite a much-vaunted integration of treatments, on the one hand we often deal with reductionist attitudes that judge psychotherapy as irrelevant and consider drug therapy alone sufficient for treatment. On the other hand, we deal with extreme psychological assumptions that consider psychiatric illness as a social problem and treatable solely – and only! – through psychosocial interventions, including psychotherapy.

Over time, psychiatry seems to move from a "brainlessness" approach to a "mindlessness" one. In fact, before the introduction of psychoactive drugs the psychiatrist's attention was almost exclusively on unconscious and intrapsychic conflicts supposed to affect the mind (as separate from the brain). After 1956, attention moved to neurotransmitters and other aspects of the brain, consequently with an extensive use of drugs and less interest for the exploration of the life stories of patients, and focused on symptoms. Therefore, a biological model of mental illness prevailed, causing an important crisis for psychotherapy [5]. In my opinion, the cause of this crisis is simple: psychiatry reductionists, using data from scientific research, support the biological causes of psychiatric illness (e.g. excess dopamine, serotonin deficiency, etc.), and therefore were supposed to be able to say when, how and why a treatment protocol is effective, describing the mechanisms of action, therapeutic effects, limitations and side effects. Is psychotherapy able to do the same?

We are faced with a potentially large misunderstanding! Marcia Angel in two consecutive defiant editorials of the New York Review of Books [6 7], meaningfully entitled "The illusion of psychiatry" and "The epidemic of mental illness", stated that when introduction of chlorpromazine in 1956, it emerged that it was able to reduce the levels of dopamine in the brain. This led to the extrapolation that schizophrenia was caused by excess dopamine in the brain. In short, instead of finding a drug to treat an anomaly, an anomaly has been postulated to justify the mechanism of action of the drug. I believe that an attitude without prejudice toward both psychotherapy and drugs should lead us to ask an important question: if data from neuroscience studies inform us about the altered substrate in a given disorder, does this explain the cause of it? This suggests paying attention to comparative studies, and leading the researchers in psychotherapy to conduct etiopathogenetic research also using important evidence from neurosciences and neuroimaging.

During the past several decades, it has become clear that all mental processes derive from mechanisms in the brain, and with the implication that any change in psychological processes is reflected by changes in the functions or structures of the brain. Several intriguing studies have shown the presence of neural plasticity within the human central nervous system; for example, the hippocampus produces cells daily and effective psychotherapy itself is able to change brain function and structure [8]. From these studies, a tendency to study the effects of non-pharmacological interventions on the brain has increasingly developed. Most studies concern the CBT; for example, randomized controlled trials (RCTs) have-supported the equiv-

alence of medication alone, psychotherapy alone and combined treatment for depression [9]. Psychotherapy in certain disorders such as OCD, major depressive disorder (MDD) and BDP provides benefits that are comparable to pharmacotherapies [10]. Goldapple et al. [11], using positron emission tomography, compared the treatment response for CBT to paroxetine in patients with MDD. They found that CBT was associated with increases in metabolism in the hippocampus and dorsal cingulate areas and decreases in the dorsal, ventral and medial frontal cortex. In contrast, paroxetine increased metabolism in prefrontal areas and decreased it in the hippocampus and subgenual cingulate. According to the authors, therefore, from an anatomical point of view, psychotherapy works through more effective "top-down" regulation, while drugs act through a "bottom-up" mechanism. Thus, different substrates can produce similar symptomatic effects!

Other studies have used emerged data to suggest the specific focus of the intervention. For example, in the case of depression, medication may help to reduce neurovegetative symptoms, and psychotherapy can reduce the distress and hopelessness [12]; integrated treatment seems superior to psychotherapy alone in those patients with a comorbid personality disorder [13].

The largest number of studies comparing "drugs versus psychotherapy" are in the field of depression, where there is much at stake considering the widespread prescription of antidepressants, even for conditions different from depression. Any balanced discussion must note that the superior efficacy of combined treatment for MDD is by no means proven. In this area, in fact, the debate has now turned very heated, particularly after the outcry following the papers by Kirsh [14-16] who argues that psychotherapy seems to have an efficacy equal to or even superior to that attributed to drugs. Kirsh, who has studied both placebo effects and the mechanism of action of antidepressants for years, has published a series of studies that criticize the way RCTs are structured. In particular, he examined 47 RCTs investigating 6 SSRIs *vs*. placebo [14]. It should be noted that Kirsch used data directly from the U.S. Food and Drug Administration, and not from published literature, since researches showing negative results are never or almost never published (as highlighted in the interesting and provocative paper by Pigott et al. [17]). His analysis shows that the improvement due to placebo was 82%, so that only 18% of the positive response is due to the SSRI. Moreover, even when the positive effect reached statistical significance, the superiority of the improvement due to the drug compared to placebo was less than 2 points in the Hamilton rating scale for depression, and thus the additional contribution to the improvement by an SSRI would be "clinically not significant" [14 18].

In a placebo-controlled trial, Beitman et al. [19] found that patients who received a benzodiazepine for anxiety and who were highly motivated to change had the most robust response. Does this suggest that *how* the doctor prescribes is actually more important than *what* the doctor prescribes? Placebo does not mean imaginary or untrue, as it produces real, clinically-significant, and objectively-measurable improvements in a wide range of conditions, including psychiatric disorders, even producing measurable changes in brain activity that largely overlap medication-induced improvements [14-16].

Some authors have recently argued that Kirsh used an analysis that relies upon an unusual technique that is biased against antidepressants, and that the data suggest that antidepressants act independently of the severity of depression, while the placebo effect is present only in milder cases. Nonetheless, the same author stressed that there is much to be learnt from Kirsh's studies, and that we need not only RCTs, but more studies in clinically-relevant populations under naturalistic conditions, for example in patients with comorbidities, considering that common clinical practice does not duplicate therapeutic procedures used in clinical trials [20]. Furthermore, while the response in the placebo group is due to unstable 'noise' and 'artefacts', the medication effect is reliable, valid and stable [21].

An important review compared the effect size of various types of psychotherapy, emerged from the main existing meta-analysis, with that of antidepressant drugs. It showed a greater efficacy of psychotherapy with an effect size of .17 to .31 for drugs, but from .62 to 1.46 for psychotherapy [22].

All this debate has great interest and is undoubtedly relevant to the entire field of mental health. However, in my opinion, the aim should be to use the data to offer to the patients the most appropriate treatment, and not to reproduce and maintain the conflict between drugs and psychotherapy that for decades has lead to inappropriate treatment or to act using an empirical logic, rather than scientific.

So is the relationship between psychotherapy and psychotropic drugs possible and, above all, useful? The difficulty in choosing the best treatment should not lead to solve the diathesis, suggesting an integration of the two treatments *tout court*. I believe that it should be clear that there is not a form of best treatment in itself, or that the integrated treatments are inherently more efficient, stated or, worse, essential for all patients, but that an appropriate choice should be made for each specific case, following accurate and rational therapeutic reasoning [23].

Integrated treatment, although more expensive in the short term, is often cheaper in the long term, given the high rate of relapse following discontinuation of psychopharmacological treatment in various diseases, for example up to 90% within 5 years for OCD, and more than 70% for panic disorder [24].

Thus, thanks to the data from scientific research, today we are able to get information, even if not definitive, about the indications and limitations of most treatments. Such information is sufficient to disregard the empirical attitude that has been widely used for several years by many clinicians, and especially psychotherapists.
Furthermore, I think that one of the most important aspects to consider is the choice of hierarchy between drugs and psychotherapy for specific psychopathological disorders, also in view of patient attitudes towards medications. This issue is very sensitive because it assigns a different role to the pharmacologist (physician/psychiatrist) and psychotherapist (physician/psychiatrist or psychologist). The prototypical example of opposing positions can be provided, in the light of evidence-based studies, on the one hand by schizophrenia and the other by DBP and OCD.
In the light of evidence-based guidelines, there is no doubt on the primary and essential role of pharmacotherapy for treatment of schizophrenia, whereas psychotherapy, particularly CBT, acts to improve treatment compliance and quality of life. Kingdon et al. [25], in a review on the combination of CBT and medication for schizophrenia, found that CBT improves the effectiveness of drug therapy alone in reducing drop-outs, increasing insight and coping. Furthermore, there are studies showing that psychotherapy focused on increasing metacognition improves work performance [26].
In the case of BPD, however, (and personality disorders in general) psychotherapy is considered the treatment of choice; increases of up to 7 times the normal rate of improvement of the natural history of the disorder have been documented, with cure rates of 25.8% per year in treated patients, compared to 3.7% of untreated patients [27].
Even in the case of PDs there are data supporting that the integrated therapy improves outcomes [28], even though the role is minimal, and evidence for pharmacological treatment of BPD are poor. Pharmacologic treatment of BPD remains preliminary despite expanding data indicating that medications alone can provide symptomatic relief. Although research continues using RCTs with a placebo arm as well as active medication arm, meta-analyses and systematic reviews have revealed that the use of any specific medication or medication class in BPD remains at best uncertain and inconclusive [29].
In OCD, RCTs have indicated that pharmacotherapies are effective only for some patients. Many patients have a good response to medication, but this is usually only a partial response. The only empirically-supported psychological treatment for OCD is CBT involving ERP. Published studies have consistently demonstrated that ERP is more effective than other forms of psychotherapy and placebos, substantially improving obsessive-compulsive symptoms with better effects compared to pharmacotherapy [4].
In light of these considerations it should be assumed that despite the fact that psychotherapy is widely used for the treatment of mental disorders, the biological equivalent of its mechanism of action are yet largely unknown. This sometimes limits psychiatrists in prescribing it, also considering the greater number of studies published on the efficacy and the mechanism of action of the drugs.
Despite advances in psychiatry and psychotherapy research, treatment outcomes are not significantly better than they were a quarter of a century ago. Treatment resistance remains a serious problem across psychiatric diagnoses. One likely reason that outcomes have not improved substantially is that as the pendulum has swung from a psychodynamic framework to a biological one, the impact of meaning (i.e., the role of psychosocial factors in treatment-refractory illness) has been relatively neglected, and psychiatrists have lost some potent tools for managing the most troubled patients [30].
A fruitful relationship between drugs and psychotherapy can only be ensured by assigning a key value to research not only for the type of therapy, pharmacological or psychological, but also for better training, both in schools of psychiatry and psychotherapy.
Psychotherapy can contribute to the exploration of the aetiopathogenetic mechanisms and have a fundamental role – as is the case with pharmacotherapy – in the treatment of mental illness only by: a) subjecting treatment protocols to scientific research in a methodologically accurate and systematic manner to assess their effectiveness; b) using the intervention techniques indicated by empirical evidence-based guidelines for a given disorder or psychopathological dimension. In the absence of these conditions, the psychotherapist likely risks to be considered as a physical therapist or a rehabilitation specialist, with a subordinate role to the psychiatrist, losing a deep understanding of the psychological mechanisms behind the suffering of patients.
This means that research should hold a core value in the background of the training of any aspiring psychiatrist or psychotherapist, otherwise leaving reductionist attitudes less open to debate and confrontation, with serious consequences for our patients. Knowledge, dialogue and collaboration are necessary to choose the most appropriate treatment for each person and considering the specific disorder.

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