

Antidepressants and psychological treatment: Hard reasons for synergy

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Abstract: Improving the efficacy of depression treatment is a clinical necessity. «Synergy» is the systematic process in which different treatments of and approaches to mood disorders are evaluated and made to work coherently to optimize their results. Depression treatment has shown to benefit from the synergy of pharmacological and psychological processes. Our aim was to evaluate present evidence as to synergizing psychological therapy and pharmacotherapy in mood disorders, reflecting the related brain systems and circulating biological substances. Multiple brain regions are involved in mood disorders, resulting in multiple-target effects of substances, each influencing neurobiological balance, and depending on individual aspects. Large studies showed that psychological treatment may, overall, be more effective than medication. However, the synergy of both provided significantly increased effects that were largely independent of each other, and each added about 50% to the overall effects of combined treatment. Identified neuropsychobiological pathways were found, as well as appreciable evidence that, in depression, the synergy of both treatments can be expected to produce better results through reciprocal effects in cortical, subcortical and visceral systems. In compromised situations such as pregnancy and adolescence, psychological treatments for mood disorders may have preference over drug treatment, but synergy remains essential.

Keywords: Depression; mood disorders; neurobiology; pharmacotherapy; psychological treatment; synergy

Antidepresivos y tratamiento psicológico: Razones contundentes para la sinergia

Resumen: Mejorar la eficacia del tratamiento de la depresión es una necesidad clínica. «Sinergia» es el procedimiento sistemático que evalúa y hace funcionar coherentemente tratamientos y/o enfoques sobre trastornos de ánimo diferentes para optimizar los resultados. El tratamiento de la depresión ha demostrado beneficiarse de la sinergia de procedimientos farmacológicos y psicológicos. Nuestra meta era evaluar la evidencia existente en cuanto sinergias entre la terapia psicológica y la farmacoterapia en los trastornos de ánimo, reflejando los sistemas cerebrales y las sustancias biológicas circulantes. Trastornos de ánimo involucran múltiples regiones del cerebro, resultando en efectos de los fármacos sobre múltiples metas, cada una influyendo el equilibrio neurobiológico, dependiendo de los aspectos individuales. Amplios estudios demuestran que, generalmente, el tratamiento psicológico puede ser más eficaz que los antidepresivos. Sin embargo, la sinergia de ambos produjo efectos significativamente mayores y en gran medida independientes, aportando ambos aproximadamente un 50% a los efectos totales del tratamiento combinado. Encontramos vías sinérgicas neuropsicobiológicas identificadas. Consta evidencia apreciable que, en depresión, es de esperar que la sinergia de ambos tipos de tratamientos produzca mejores resultados por sus efectos recíprocos en sistemas corticales, subcorticales y viscerales. En situaciones comprometidas, tales como el embarazo y la adolescencia, los tratamientos psicológicos de los trastornos de ánimo pueden merecer preferencia sobre el tratamiento con fármacos, pero sinergia sigue siendo esencial.

Palabras clave: Depresión; trastornos del estado de ánimo; neurobiología; farmacoterapia; tratamiento psicológico; sinergia

Recibido: 09 de octubre 2020; aceptado: 10 de febrero 2021

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Introduction

Present pharmacological treatment of mood disorders with antidepressants and anxiolytics

is primarily and routinely directed at modifying levels of specific mood-related substances and has predominantly corticolimbic effects (Messina, Sambin, Palmieri, and Viviani, 2013). Thus, a prime effect is facilitating functionality. However, a brain thus treated with psychoactive substances may be functional but has not regained previous «normality». Opinions and study results differ as to which antidepressant is most effective and rankings not necessarily contemplate side effects (Cipriani et al., 2018). Differently, psychological treatment of mood disorders results in lasting psychobiological normality. Synergy, as the intended and *structured* application of both pharmacological and psychological treatment, as required, aims at comprehensive results, short and long-term. It may be considered a form of transdiagnostics (Sandín et al., 2012). Synergistic approach has a neurobiological basis. Synergy has been recognized as an essential component of modern psychiatry (Nasrallah, 2006). Nevertheless, heralded advances in depression treatment are typically limited to pharmacotherapy or biological methods, obviating proven psychological approaches (Licinio & Wong, 2020)

Still, at present, clinical treatment of mood disorders either centers on psychological treatments or favors pharmacological remedies that are incidentally supported by psychological treatment. Each proved measurably and comparably effective but they differ in long term results and in side effects. One cause for differences lies in their different loci of action. The heterogenic interrelation between mental states and physiological parameters has become clearer (Gevins et al., 2002, Wilkinson et al., 2019). Some 1500 identified different combinations of behavioral and neurobiological symptoms for major depressive disorder alone result in a need for markedly different treatment approaches (Sharpley and Bitsika, 2013).

In our context, synergy is the systematic process evaluating different treatment options or agents and their intended simultaneous application aimed at enhancing their cumulative function and effects. This implies optimizing combinations of treatments individually, including lifestyle changes. Synergy is therefore more than adding «other» treatment elements on a chance of adding value. In mood disorders, synergy may improve the comparable efficacy of antidepressants and psychotherapy, hence mental health services worldwide are developing more synergy (Ellis et al., 2017; Hannigan et al., 2018). Increasing intercare collaboration, although not yet the same as collaborative care, was found to favor efficiency, care quality and adequate professional training, but synergy goes further.

Synergy: principal observations

Clinical treatment dilemmas are frequent in mood disorders. The existing divergence of treatment propositions for mood disorders also differently prepares medical and psychology professionals. Research results are ambivalent because, in mood pathology studies and depending on design and patient characteristics, either pharmacological treatment or psychological treatment resulted more effective. In depression, combining treatments favored results. A timid consensus is forming that both therapeutic approaches should be coordinated from inception to warrant more positive results in the long term (Cuijpers et al., 2014; Roiser, 2015; Seeberg et al., 2018; Davidson, 2010). However, insufficiently unified criteria complicate combination protocols.

In combined treatment application, timing of intervention elements is of importance. An optimal protocol requires previous diagnoses integrating neurobiology, psychiatry and psychology, considering clinical availability, cost and patient characteristics. The physician may consider pharmacology and not psychotherapy. In turn, psychologists may find psychological treatments a better fit.

Health authorities and organizations are aware of this problem but consensus on the necessary bridging strategies is still lacking. Moreover, availability or cost of psychological treatment may be obstacles, although less costly internet-assisted protocols show positive results (Thase et al., 2018, Cuijpers et al., 2019), also in primary care (Høifødt et al., 2013).

The Lancet Psychiatry Commission affirmed in 2018: «The combination of psychological and pharmacological treatments needs to be better understood, both in terms of the clinical effect and the underlying shared and different mechanisms» (Holmes et al., 2018). However, said statement surprisingly purports that the goal of adding psychotherapy to pharmacotherapy should be «remov(ing) a barrier to successful treatment with an antidepressant drug», whereas a primary goal of mood disorder treatment should be treating depression without creating any (antidepressant-) dependency (Moncrieff, 2016). Also, the statement classifies psychotherapy as a mere auxiliary to antidepressants which disregards synergy's – demonstrated - axiom that treatments are of equal value (Kappelmann et al, 2020). Authoritative comparisons admit that psychological treatment may, overall, be more effective than medication: 54 % improved with antidepressants, 62% with psychological treatment (Cuijpers, Stringaris & Wolpert, 2020).

Neurological balance and mood disorders

Causes and consequences of mood disorders always combine biological and psychological elements. Treatments limited to pharmacology reflect a materialism wrongly presupposing mental events to be reducible to biological (brain) events. Behavioral neuroscience or psychobiology, and especially psychoneuroimmunology, provide clinical data as to optimal system interactions requiring combined treatments. In clinical practice, psychiatry and psychology are not yet at synergy, however, although neuroscience brings increasingly solid data in favor of their greater synergy. Neurobiological pathways and mechanisms in any mood disorder are never unique or linear. Substances involved, sites of action, and repercussions in other neuronal events are complex but knowable (Sharpley and Bitsika, 2013).

Psychological and biological components of a mental disorder alter neurochemical balance by diverse mechanisms. Implicated neurotransmitters are monoamines, gamma-aminobutyric acid (GABA) and glutamate, but also many other modulators including adenosine, cannabinoids, neuropeptides, hormones, neurotrophins, nitric oxide, cytokines and different cellular modulators. Genetics do play a role (Liu et al., 2018). All biological and psychological reactions are measurably manifest in different brain structures. In anxiety or depression, antidepressants reduced activity in the right paracingulate region whilst psychotherapy did the opposite and increased activity, interpreted as a top-down intent to correct the abnormal corticolimbic brain activity caused by the disorder (Kalsi et al., 2017). Also, functional magnetic resonance imaging (fMRI) showed that pain is expressed in the same place of the brain irrespective of its origin in a physical or a psychological event (Eisenberger, 2012). Thus, the brain does not *functionally* distinguish between noxious stimuli of biological or psychological origin. Subjects could be trained to mentally re-categorize sensations, for instance to reframe pain as a pleasant experience, independently of the opioid system, and clinical use of psychological mental imagery techniques for re-categorizing symptoms has been found clinically effective (Berna et al., 2018). Stress is another example of this bifocality. Diverse neurological alterations provoked by stress are identified both in animal and human models and impact on virtually all systems: motor, sensorial, endocrine, immune, cardiovascular, neural, and psychological (Kumar et al., 2013).

The psychological significance of interventions that mitigate non-emotional symptoms of anxious states such as chronic pain, cardiovascular conditions and a

variety of somatic complaints is a given (Millan, 2003). Brain circuits relevant for both emotional and cognitive components of depression and anxiety are especially relevant. Several limbic and cortical structures are involved in mood and mnemonic mechanisms (Gray, 1987). Apart from the limbic system – predominantly the amygdala, hippocampus and the periaqueductal grey – the stress response and its control receive significant though sometimes counterposed contributions from nearly all cortical regions (insular, orbital, entorhinal, temporal, associative, frontal, pre-frontal, cingulate, parietal and visual) (Groenewegen and Uylings, 2000, Pralong et al., 2002; Hurley et al., 1991). One consequence of this multi-input is significant inter-individual differences of clinical relevance. For example, 80% of depressed persons show elevated cortisol (Thompson and Craighead, 2008) but 20% do not, thus hypothalamic-pituitary-adrenal (HPA) hyperresponsivity is not universal among depressed patients. In short, multiple regions are involved in mood disorders, resulting in multiple-target effects of substances, each influencing neurobiological balance (Hindmarch, 2001).

Emotion and cognitive processes are confirmed to have a different basis, emerging from systems that generate an «instinctive» action from visceral homeostatic interoceptors, predominantly in *subcortical* regions (Panksepp, 2003). These large but slow-acting systems generate the «intentions *during* the action» and generate «raw» affective states independent of cognitive mechanisms (Searle, 1983). On the other hand, cognitive processes relate to sensorial exteroceptive systems, with mechanisms of fast neuronal action with little intrinsic affective content that produce the «intentions *of* the action» (Heyes and Dickinson, 1990). They generate affective sentiments in specific subcortical circuits where slow-triggered neural systems proliferate with an ample presence of neuropeptides, widespread in the visceral nervous system (Panksepp, 1993, 2010). Emotional responses probably surge from medial limbic regions of the neuroaxis. Thus, emotional processes relate more with viscera-neuropeptide systems than with somatic functions of the brain and rapid-rate Magnetic Transcranial Stimulation (rTMS) - an alternative therapy with strong indirect effects on subcortical processes - emerged as a non-invasive intervention for depression (Teng et al., 2017; Mishra et al., 2011; Berlim et al., 2013), and possibly for stress (Hedges et al., 2003). Thus, mood disorders implicate multiple regions, multiple substances and multiple targets but, moreover, the emotional and cognitive brain processes involved are essentially different, a fact that treatment should target.

Inherent limits on the effects of psychoactive medication

Cognitive system research is producing new data on the scope of linear action drugs, widely used in mood disorders. As said, neurotransmitters and receptors may mediate *opposite* actions depending on their place in different brain structures; of their pre- or postsynaptic presence; the duration of their activation; and the type of mood disorder involved. However, *different* neuromodulators may have a *similar* influence on mood states as the result of synergous action in multiple loci. For example, substances that reinforce GABAergic transmission in the amygdala reduce anxiety, whilst exciting neurons that contain corticotrophin liberating factor (CRF) have the opposite anxiogenic effect (Zeng et al., 2003). Surprisingly, improving the liberation of serotonin (5-HT), noradrenalin (NA) or dopamine (DA) proved not to be synonymous of an anxiolytic consequence, nor does its reduction warrant anxiogenic consequences (Millan, 2003). Anxiolytic and anxiogenic consequences are therefore independent of the circulating quantity of said monoamines. Notwithstanding these uncertainties, manipulating their release is still the essence of antidepressant treatment, (Joca et al., 2015).

When evaluating the efficacy of therapy, we need to integrate essential concepts:

- (1) Neurotransmitters and other modulators present high levels of co-storage and co-liberation and operate in a coordinated and dependent way (Jing et al., 2001; Blank, Nijholt, Vollstaedt, et al., 2003; Blank, Nijholt, Grammatopoulos, et al., 2003; Hnasko and Edwards, 2012; Merighi, 2018). At the synaptic level of specific neurons, multiple transmitters and receptors interact (cross talk). Interrelated receptors not only interact with intracellular messengers but physically associate to form heterodimers with functional properties that differ from their homomers. In laboratory cultures, the assembly of functional heterodimeric adrenergic, serotonergic, dopaminergic, opioid, and adenosinergic receptors has been observed (Maggio et al., 1993; Pan et al., 2002). Heterodimeric structures in the brain and their cross talk are common for serotonin and glutamate (Wischhof and Koch, 2016, Halberstadt et al., 2019) and opioids (Fujita et al., 2015).
- (2) The activation of a specific receptor does not always produce the same effect. Certain antidepressant drugs may favor the activation of one in many different alternative intracellular «cascades», whilst coupled to the same receptor. These cascades may have different

associations of beneficial properties and adverse effects (Kenakin, 2002; Hunyady et al., 2003). Cascades from certain natural antidepressants such as hyperforin have also been observed (Bouron and Lorrain, 2014).

- (3) Any linear actuation of drugs may be nullified by «constitutionally active» receptors: those that show spontaneous linking to G proteins (Millan et al., 1999). These receptors act as «inverted agonists,» annulling the activity of agonists although the effects of both may be blocked again by «neutral» antagonists (Seifert and Wenzel-Seifert, 2002). With heterologous receptors - those activated by more than one substance - the activation of inverse agonists may be more efficacious than the use of neutral antagonists. Animal studies confirm the effects of inverse agonists on depression and brain substance homeostasis (Iida et al., 2017).

These data transmit an important message to the clinician. Given the intimate, complex and reciprocal interactions between biological parameters and mood states as integrated and modulated in structures such as the amygdala, the hippocampus and the cortex (McKell-Carter et al., 2003), it is improbable that any pharmacological substance could influence mood profoundly and foreseeably over the long turn. However, psychological mechanisms will influence both mood and biological factors.

Interactions and multiple controls

This amalgam of counterposed cortical, limbic and subcortical influences makes regulation and stability of clinically manifest functionality depend on a hierarchy of controls. Substances that alter mood also influence cognition, motor behavior, nociception, endocrine secretion, and emotion. Mood modulation may only be a secondary effect. This intracellular phenomenon of «exaptation» exists in receptors, neurotransmitters, neurons and brain circuits and may constitute the evolutionary foundation of the central nervous system.

All brain modulators interact, and their functional properties reflect over time and space. At most, the individual components of mood state networks may disclose a partial explanation of underlying mechanisms. The multiplicity of endogenous mechanisms of mood changes indicates that lasting therapeutic efficacy of drugs interacting with just one mechanism is questionable. Agents affecting two or more mechanisms should have a better therapeutic efficacy, for example those that reinforce endogenous anxiolytic mechanisms whilst inhibi-

ting anxiogenic factors. However, therapeutic targets that combine corticolimbic and subcortical mechanisms may obtain better and lasting results. Psychological treatments showed to influence more substances than antidepressant monoamines, consequently:

- (1) Affective-emotional states relate to cortical neurotransmitters but also to other substances with cortical, subcortical and visceral action, with multiple interrelated consequences, yet to be completely identified and understood.
- (2) These substances respond to balancing mechanisms of a biological and of a psychological nature, each often requiring holistic adjustment.

Autonomous value of psychological treatment in mood disorders

The aforementioned mechanisms indicate that the treatment of mood disorders exclusively with psychoactive medication has inherent limitations.

Re-establishing mood-related normality implicates multiple substances and structures, as indicated above. This goal is not likely to be obtained with drugs acting on one or two neurotransmitters (Ressler and Nemeroff, 2000), nor is a brain on antidepressants the same as a brain without depression (Willner et al., 2013), hence the need for synergistic approaches. Systematic synergy between psychological treatment and drug treatment does not mean that drugs must always be used, but that both aspects need always be evaluated, and psychological treatment always accompany. In recent decades, specific psychological therapies proved more efficacious. The response of selected neurotransmitters to psychological treatment was less solid than obtained with specific antidepressants, but a definable positive correlation was established (Van der Pompe et al., 2001; Niemeier et al., 1999; Karlsson et al., 2010).

A positive neurobiological impact of psychological treatment on serotonin or the glucose metabolism was established (Karlsson et al., 2010; Kennedy et al., 2007) Functional and rest MRI, but also newer voxel-based positron emission tomography (PET) identified brain regions affected by depression and showed the changes in active substances as a result of therapy (Linden, 2006). All studies underline a notorious individual variety as to affected areas (Diener et al., 2012; Müller et al., 2017).

As said, pharmacotherapy may facilitate functionality without re-establishing overall normality, as it modifies the *manifestations* of neurochemical imbalance of the disorder (bottom-up), requiring prolonged treatment to reduce the risk of relapse. Even then, drugs do not

necessarily re-establish normal or pre-disorder levels of target substances, but rather facilitate the brain's functionality whilst it attempts to regain neurobiological normality by its own means. Psychological treatments have proved to serve this last purpose. Their (top-down) effects affect many neurobiological substances. In depression, therapy measurably changed long-term levels of neurotransmitters, neurosteroids, and a plethora of other substances (Honeyman, 2016).

Clinically, concurrent and synergic application of both approaches still needs time. Antidepressants may need up to ten weeks to reach therapeutic efficacy (Trivedi et al., 2006). Psychological treatments may need a similar time, but a strong early response is obtained in a significant number of cases (Lambert, 2005) thus early initiation is recommended. The person's functionality may start to improve with antidepressants before psychological treatment commences (Petersen, 2006) although this is questioned. Psychological treatment ab initio may advance positive results by 3 to 6 weeks. Psychological treatment was found to enhance the effects of antidepressants and improve patients' long-term prognosis (Hollon et al., 2005), although with several observations. In their 2014 meta-analysis of 52 studies, $N= 3,623$, Cuijpers and colleagues found that adding psychotherapy to drug therapy in depression and anxiety disorders provided «effects that were largely independent of each other, and each add about 50% to the overall effects of combined treatment» (Cuijpers et al., 2014). This moderately large effect and clinically meaningful difference in favor of combined treatment lasted for at least two years after treatment. Also in 2014, a Cochrane systematic review on children and adolescents indicated similar provisional results (Cox et al., 2014). However, we should not conclude that adding psychoactive medication is «boosting the effects and retention of psychological interventions», as the Lancet Commission affirms. Both treatment types have their reasons and mechanisms, are of equal value, and positive treatment results depend on synergetic clinical strategy.

Special importance: Mood disorders in vulnerable cohorts

Consideration is required with special cohorts such as adolescents and perinatal women. Side effects of antidepressants preoccupy and, although medication should not be excluded for specific cases, alternative treatments are to be actively preferred (Campagne, 2019).

In adolescents, but also in adults, selective serotonin reuptake inhibitor (SSRI) antidepressants, especially

citalopram, was argued to substantially increase the risk of suicide and a Federal Drugs Administration (FDA) black-box warning was issued in 2012. Their use should be avoided when valid alternatives are available. A recent small study establishing the contrary does not yet cancel this black box warning.

Conclusion

Depression is the world's third leading cause of years lived with disability (The Lancet, 2018). Thus, the search for highest possible efficacy of treatment is a global concern.

Neuropsychobiological research confirms that mood disorders produce simultaneous, overlapping and counterposed effects in various neural systems both at corticolimbic and subcortical as well as at visceral or endocrine levels (Marwood et al., 2018). As present, pharmacological antidepressant and anxiolytic treatments predominantly aim at corticolimbic functioning, and do not aim to produce necessary subcortical or visceral adjustments. A synergic combination of pharmacotherapy and psychological treatment has more complete effects, leading to earlier remission of symptoms and regaining neurobiopsychological stability.

Importantly, biological and psychosocial factors are not dichotomous but are concurrent mechanisms, where the need for synergy of psychotherapy and pharmacotherapy is supported by different neural mechanisms, as brain imaging studies show (Dean and Keshavan, 2017; Goodwin et al., 2018; Boccia et al., 2016).

Synergy is defined to be always intentional and requires early coordination of pharmacological and psychological treatments and a therapeutic protocol contemplating both treatment approaches, requiring paradigmatic protocol changes and recognizing the relevancy of neurobiological processes underlying mood disorders. For the clinician, synergy is not just an option but an important tool. This does not mean that both treatments should always be applied together. Both aspects should be evaluated (Garland et al., 2016). However, recent quality studies and meta-analysis indicate that combined therapies are – in general – significantly more effective in mood disorders (Cuijpers et al., 2020).

Research suggestions emerge from the above. Establishing the efficacy of each specific pharmacological or psychological treatment is important, but not enough (Moriana & Martinez, 2011). The concurrent efficacy of both treatments and their neurobiological processes need further clinical definition, resulting in recommendations

for synergic mood disorder evaluation protocols and treatment. Normative guidance on neurobiological factors in mood disorder treatment could unify clinical criteria.

Conflicts of Interest

The author has no conflicts of interest to declare

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