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Neural Implications of Psychotherapy, Pharmacotherapy, and Combined Treatment in Major Depressive Disorder

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ABSTRACT

Numerous clinical trials have been conducted to determine the utility of antidepressant treatment (ADT), psychotherapy, and combined psycho-pharmaco-psychotherapy (PPPT) in treating major depressive disorder (MDD). While all approaches have shown benefit over placebo to varying degrees, the parallel neurophysiological mechanisms that underlie their efficacy have received little attention. The authors will review and discuss a growing body of literature that relates the factors of treatment selection and response to the principles of neuromodulation, with emphasis regarding how neuroimaging and other experimental data reinforce the need for personalized MDD treatment. This manuscript and its theoretical approaches were supported by conducting relevant literature searches of MEDLINE and PubMed electronic databases, prioritizing systemic reviews, and randomized clinical trials using selected MeSH terms. The authors conclude that ADT, psychotherapy, and PPPT all create potentially observable neurofunctional changes and argue that additive and synergistic potentiation of these effects in PPPT may produce more sustained symptom relief than with monotherapy alone.

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Introduction

Major depressive disorder (MDD) is among the most commonly diagnosed and treated of all psychiatric disorders. More randomized controlled trials (RCTs) have been conducted to elucidate therapeutic options for MDD than perhaps any other mood disorder. Nevertheless, MDD remains difficult to treat for the precise reason that it has been historically difficult to characterize: it is a fluid mood disorder with a wide range of fluctuating symptoms, whose course and severity almost always differ from patient to patient. Other psychiatric illnesses share this protean quality, but the combination of high prevalence, broad symptoms, and dynamic course makes MDD uniquely intractable for some patients. This reality has unfortunately been stigmatized by some who likened MDD management to mere educated guesswork regarding the selection of treatment alternatives.

Fortunately, however, MDD research has rapidly progressed on the heels of better technology and imaging techniques. The inherently illusive nature of bio-behavioural mechanisms, while still illusive, has yielded enough insight to provide patients with concrete pharmacological and psychotherapeutic options of unquestioned benefit. Integrated or combined treatment, here termed psycho-pharmaco-psychotherapy (PPPT), has proven especially useful in selected subgroups of MDD patients. The authors wish to discuss the current standard of care for MDD, including antidepressant treatment (ADT), psychotherapy, and PPPT, in light of the underlying neuromodulatory principles gradually gleaned from years of research and experimental data. The authors hope to describe how the psychotherapeutic trial and error process, in contrast to what may be a public misconception, is not a fallback used by the unskilled clinician, but rather a methodical, scientific, and experience-driven approach that capitalizes on additive neuromodulation of different treatment modalities. The paper begins by introducing the heterogeneous nature of MDD and covers, in sequence, patient-related factors involved in treatment selection, recently discovered neural correlates of treatment response, and a brief review of the major studies conducted on the efficacy of PPPT. Finally, special consideration is given to the neurofunctional changes elicited by these treatments which, taken together, form an intuitive yet biologically framed picture suggesting the theoretical utility of, and clinical rationale for, the use of PPPT in certain patients.

The search strategies employed in this review included relevant literature searches of MEDLINE, PubMed, and PubMed Central online databases. The following MeSH terms were used: depression, pharmacotherapy, psychotherapy, and neurobiology. Systematic reviews and meta-analyses were prioritized for inclusion, followed by RCTs. In addition to using PubMed's "similar articles" function to find related material, each article's bibliography was reviewed for potential research findings relevant to these terms.

Knowing Major Depressive Disorder: A Protean Illness

The diagnosis of MDD is complicated by a myriad of heterogeneous symptoms that cannot be simply explained by neurotransmitter imbalances. Treatment with a single ADT agent (such as a selective serotonin reuptake inhibitor [SSRI]) to improve these potential imbalances among heterogeneous MDD patients (melancholic, atypical, seasonal, vegetative, and agitated) is likely not enough for most individuals. If this were enough, clinicians would need only to prescribe one antidepressant for all patients to bring about remission. The standard US Food and Drug Administration (US FDA) drug approval process often fails to account for disease heterogeneity because of the difficulty inherent in evaluating a nonspecific treatment, i.e., treatment that cannot be definitively designed and targeted for a particular, uniform disease. Unfortunately, the belief that MDD is a uniform disorder is a naïve view that clinicians know rarely holds true in practice, despite the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) (American Psychiatric Association, 2013[1]) defining MDD as a collection of separate symptoms that together form a homogeneous syndrome. While the US FDA recognizes only studies conducted on one specific syndrome or medical illness, it is not uncommon for a particular psychiatric condition to present as one of the several diverse subtypes depending on the patient's unique combination of psychosocial, behavioural, physiological, or other determinant signs and symptoms. The brain and its neuroarchitecture are not organized by the DSM criteria, and when different neural pathways misfire, different symptoms may occur. In the case of MDD, this likely allows for the different subtypes of depression or different symptom experiences for each MDD patient (Stahl, 2013[37]).

Studying Major Depressive Disorder: Insights of Neuroimaging

While the subtypes of MDD, or MDD symptom clusters (e.g., melancholia), may be studied from a study population perspective, an even more descriptive approach employs both genetic and neuroimaging techniques to gather information on whether or not specific neuroanatomic brain areas are functioning normally. In this model of study, MDD symptoms that a patient exhibits

externally would be considered their phenotype. ADTs, as biological agents, can directly affect a wide range of central nervous system entities including neurotransmitters, transporters and enzymes. Changes in these entities may influence the electrical state of malfunctioning brain areas to the extent that these areas' respective functions can be normalized or improved. These changes in brain function represent endophenotypes and may be scanned and measured via functional brain imaging studies (e.g., functional magnetic resonance imaging [fMRI]). In an effort to homogenize future ADT-based RCTs, researchers may strive to use fMRI procedures during patient recruitment such that patients' external symptoms (phenotype) and internal brain state descriptors (endophenotype) may be matched upon study entry and the ADT effects are more reliably measured (Schwartz, 2013[34]).

As will be discussed later, functional neuroimaging also lends itself to determining how psychotherapy, pharmacotherapy or PPPT can alter depressive brain function during treatment and after remission. These biological findings may then be compared and contrasted to better determine how each treatment modality affects specific brain areas.

Treating Major Depressive Disorder: Predictors of Patient Response

In deciding the most effective course and type of MDD treatment, numerous elements must be taken into account by the clinician, including, pivotally, the severity of the current major depressive episode (Thase *et al*., 1997[44]). In light of some meta-analyses suggesting that ADTs may offer little efficacy above placebo (Kirsch *et al*., 2008[20]), researchers and clinicians were prompted to revisit how RCTs in the modern era are conducted. They came to the consensus that antidepressants are generally more effective in treating those with severe MDD and that placebo effects are often greater in those with milder MDD. Nevertheless, the current trials continue to enroll a disproportionately high percentage of mild-to-moderate depressives. To avoid the possibility of excessive placebo effects in RCTs, researchers should aim to involve the more seriously depressed patients and allow more time for possible changes in patients' depression ratings, which would improve statistical power and stringency.

Some authors strongly suggest that depressed patients with pathologic personality traits often have a decreased response to psychopharmacology alone compared to those without personality disorder symptomatology (Reich and Vasile, 1993[32]; Thase, 1996[42]; Gorwood *et al*., 2010[13]; and Takahashi *et al*., 2013[41]). Therefore, the presence, chronicity, and severity of marked maladaptive personality traits together comprise yet another important variable influencing the efficacy of ADT in MDD, one often indicative in the practice of treatment resistance and MDD recurrence. Patients with "Cluster A or Cluster

B" personality pathology appear to have less satisfactory results to medication management, whereas those with Cluster C symptoms tend to do better (Wilberg *et al*., 1998[47]; Peselow *et al*., 1994[31]; Maddux *et al*., 2009[24]; and Moradveisi *et al*., 2013[27]). It also appears that MDD patients who have suffered trauma or abuse may preferentially respond to PPPT, whereas those without a trauma history appear to do well on an ADT alone (Nemeroff *et al*., 2003[28]).

MDD severity and personality variables are presented to begin the discussion regarding the neurobehavioural aspects of antidepressant choice and treatment. There are likely many other factors involved in treatment planning that may affect outcome (e.g., comorbidity with substance use disorder, anxiety disorder, previous history of trauma, etc.). Oftentimes, ADT are chosen based on their US FDA indication for the treatment of MDD, but also depending on the prescriber's interpretation of severity, comorbidity, and specific MDD symptoms targeted for amelioration. This patient-individualized approach to treatment runs counter to the more generalized US FDA drug approval process, wherein all antidepressants that have proven safe and have overcome the placebo effect in at least two RCTs are given the US Federal imprimatur. This basic approach would be based on the US FDA suggestion that all antidepressants are equal and that no single ADT can market itself as having greater efficacy than any other ADT, a standard which has existed since imipramine was approved several decades ago. This approach errs in assuming that all MDD patients are the same, both phenotypically and aetiologically, and ignores the importance of personalised, neurobehavioural patient assessments in the art of prescribing ADT.

Targeting Major Depressive Disorder: Neural Correlates of Depression

MDD patients who undergo functional brain neuroimaging often show a decrease in activity in the dorsolateral prefrontal cortex (DLPFC), correlating with an increased symptom severity (Brody *et al*., 2001[3]). Stahl (2003[36]) suggests that hypofunctioning in the DLPFC may lead specifically to fatigue, poor concentration, and executive dysfunction which are often seen in MDD patients. This brain area is rich in glutamate, norepinephrine, and dopamine activity. While a prescriber could choose any US FDA antidepressant to treat MDD, prescribing exclusively an SSRI may not make intuitive sense if symptoms of DLPFC hypofunction are present. An astute prescriber may preferentially choose an antidepressant with more norepinephrine facilitation, such as a serotonin–norepinephrine reuptake inhibitor or a norepinephrine–dopamine reuptake inhibitor. These types of antidepressants specifically target noradrenergic neurochemistry in the DLPFC and may be theoretically more effective in MDD patients with fatigue and executive dysfunction. This claim is supported by human ADT data as well as data from several case series (Katz *et al*., 2010[19]), which suggest that certain off-label attention deficit hyperactivity disorder

(ADHD) type stimulants may be justified in the treatment of MDD based on their DLPFC-specific pharmacodynamic properties, even while their evidence base in MDD treatment is weak compared to SSRIs. The stimulants are robust in the facilitation of frontocortical norepinephrine and dopamine activity and clearly target and improve the indicated fatigue and ADHD symptoms. MDD patients with DLPFC-related symptoms who are treated with stimulants instead of ADT may experience symptom relief as long as the stimulants manipulate the neurotransmitters needed to restore normal brain functional activity.

Psychotherapy may affect DLPFC functioning and treat associated MDD symptoms in a way that is similar to the aforementioned ADT classes. A review by Frewen *et al*. (2008[10]) discusses the impact of cognitive behaviour therapy (CBT) and interpersonal psychotherapy (IPT) skill training used to enhance coping, problem-solving, and interpersonal functioning in MDD. Prior to behavioural intervention, patients had exhibited external phenotypic symptoms of MDD while imaging studies revealed a concurrent endophenotype of a hypofunctioning DLPFC. After intervention with one or the other therapy, enhanced DLPFC functioning was observed. Since ADT was not prescribed, it must be hypothesized that psychotherapy promoted corrective neurofunctional changes. These types of studies provide evidence that the MDD brain can return to normal electrophysiological functioning (a normal endophenotype) after treatment with psychotherapy, ADT, or PPPT, and thus allow for a normal external phenotype (nondepressed or euthymic) to be expressed.

Outside of a hypofunctioning DLPFC, the limbic system is also implicated as being abnormal in MDD pathophysiology. Dichter *et al*. (2009[8]) found that MDD patients treated with behavioural activation techniques had significant MDD symptom improvements that were associated with increased responsiveness in the limbic reward centers of the brain. In contrast to the above DLPFC findings, these limbic findings may be associated with different MDD symptoms such as drive, initiative, and enjoyment. Again, different ADTs may be better suited for treating MDD symptoms associated with limbic malfunction. It is possible that behavioural therapy, more than cognitive therapy, may work in this context.

Information about the functional state of these neural correlates in an individual patient would be extremely useful for the clinician in light of the heterogeneous nature of the disease, and would add an important tool to facilitate treatment selection. Choosing an ADT monotherapy or psychotherapeutic technique could thus be based not solely on generic FDA indications or specific RCT data in patient subpopulations, but also, more specifically, on the endophenotypic findings revealed by the available neuroimaging studies that correlate with a patient's phenotypic presentation. For example, a recent study by McGrath *et al*., 2013[26] to identify potential neuroanatomical biomarkers for MDD treatment selection revealed a robust correlation between right anterior insula metabolic activity (evidenced by PET) and depressive remission (≥7 on

the Hamilton Depression Rating Scale). Interestingly, insula activity appears to be positively correlated to ADT remission yet inversely correlated to CBT remission. In other words, insula hypometabolism is observed with remission to CBT but poor response to ADT, while insula hypermetabolism is observed with remission to ADT but poor response to CBT. In the future, clinicians may be able to draw on similar data to more accurately choose the most effective ADT and/or psychotherapy for their patients, relying on neuroimaging rather than isolated clinical trial data or the "best-guess" psychopharmacodynamic approaches.

Prescribing Polypharmacy: Complementary Mechanisms

Prescribers are sometimes accused of abusing the technique of polypharmacy, in which ADT monotherapy is abandoned in favour of combining multiple ADTs at once. Oftentimes, polypharmacy is used in patients with high levels of comorbidity and treatment resistance or other cases where the FDA and RCTs cannot provide an adequate evidence base from which to guide clinical decision-making (Schwartz and Rashid, 2007[33]). This rational polypharmacy approach is based on the idea that the right combination of ADTs will likely affect complementary neurotransmitter arrays and, in turn, multiple brain areas, each responsive to one or more neurotransmitters (Stahl, 2000[35]; Stahl, 2013[38]; Topel *et al*., 2011[45]). The same line of reasoning may apply to PPPT as well in explaining its potential synergistic effects.

Take for example the treatment of initially resistant MDD, where a patient is only partially better while taking an SSRI monotherapy (i.e., serotonin manipulation only). Most guidelines and clinical practitioners would not advocate combining two mechanistically similar SSRI antidepressants. One reason is the risk of serotonin toxicity adverse effects, but another is common sense: if the patient is not responding to a full-dosed SSRI, why should a second SSRI, acting on the same neurotransmitter via the same mechanism of reuptake inhibition, be any more effective? Most clinicians would likely combine or augment the SSRI with an agent that elevates neurotransmitters other than serotonin. Supporting this claim is a recent review by Wang and Pereira (2016[46]), who conclude, based on findings suggesting the distinct neuromodulatory action of these neurotransmitters (serotonin, norepinephrine, dopamine, and acetylcholine) that each should be viewed as separate yet interdependent contributors to affective state dynamics. The authors propose a two-gradient system, wherein dopamine and serotonin, at opposite ends, co-regulate one affective gradient (pleasure–displeasure), while norepinephrine and acetylcholine, in a similar manner, co-regulate another (surprise–anticipation). The grid that results from the intersection of these two theoretical axes provides a simplified yet useful conceptual space for understanding how complex emotions might arise from an interplay of basic affective states, analogous to the way in which, in colour theory, a variety of hues can be generated from a mix of just three primary

colourants. Ideally then, in the context of this proposed framework (which future study might yet enhance and refine), a clinician's decision to modify the activity of a particular neurotransmitter may reflect a deliberate calculation, not mere guesswork, based on the patient's "location" within this emotional/affective "matrix." In a similar vein, the addition of psychotherapy, either simultaneously or sequentially as PPPT, makes sense if one considers that the SSRI is likely improving limbic brain area functioning while IPT or CBT may concurrently improve DLPFC functioning. This approach would allow for two theoretically dysfunctional brain areas to be aggressively treated at once with two robust treatment modalities.

It is worth noting the futility of continuing years-long psychotherapy if such therapy has failed to yield remission by a certain time point. Therapists should consider in these cases the fact that focal use of one modality is likely to affect just one specific set of neurocircuits. In the absence of full remission, there may be other neurocircuits worth attempting to manipulate through ADT augmentation, switching of the ADT, changing psychotherapy style, or applying PPPT. This theoretical, polytherapeutic approach would be neurologically comparable to the rational polypharmacy that a prescriber may employ.

Considering PPPT: A Brief Review of the Literature

Comparing the impact of PPPT to monotherapy necessitates an appraisal of the literature. To begin with, two studies by de Jhonge *et al*. will be discussed. In their first study (de Jonghe *et al*., 2001[6]), the authors found that PPPT (defined as psychodynamic supportive psychotherapy plus ADT) was more effective than pharmacotherapy alone in treating MDD. At 24 weeks, the mean success rate in the PPPT group was 59.2% compared to 40.7% for ADT alone. The second study (de Jonghe *et al*., 2004[5]) analyzed short-term psychodynamic supportive therapy alone versus combined with ADT (i.e., PPPT) and found no major group differences. However, subjective patient responses were statistically significant for greater symptom improvement in the PPPT group. This particular study did not have a psychopharmacology only arm, and patients were allowed to choose not to be involved in the combination treatment arm due to fear of medication side effects, restricting comparative analysis and possibly leading to a biased sample. Kool *et al*. also utilized a PPPT approach and demonstrated its superiority to monopharmacotherapy. PPPT in this study was more effective in MDD patients with coexisting personality disorders than those without (Kool *et al*., 2003[23]). The National Institute of Mental Health Sequenced Treatment Alternatives to Relieve Depression trial and others suggest that psychotherapy added after incomplete initial ADT response may provide a greater impact on clinical symptom reduction than medication alone (Harley *et al*., 2008[14]; Thase *et al*., 2007[43]). The Research Evaluating the Value of Augmenting Medication with Psychotherapy trial also evaluated MDD patients with incomplete

ADT responses. It sought to compare the augmentation of antidepressant nonresponse elicited by two PPPT strategies that differed only in the type of psychotherapy employed (e.g., manualized psychotherapy treatment vs. treatment-as-usual supportive psychotherapy). The authors determined that neither specific type or style of augmentation psychotherapy nor continued ADT alone significantly improved MDD outcomes from a superiority point of view (Kocsis *et al*., 2009[22]).

The above mentioned studies, sometimes conflicting, raise doubts about research methodology: it is intrinsically difficult to construct an internally valid study with the power and factorial design needed to properly compare multiple interventions. That goal becomes almost prohibitively difficult in the context of a disease as protean as MDD, in which ideal stratification of the intervention group (to control for any number of disease variables, e.g., severity, aetiology, and recurrence) greatly increases the requirement for statistical power. Few institutions have the resources or capability to recruit as many study patients as would be needed to achieve that requirement, and so the majority of research findings cannot be viewed as supplying definitive evidence for or against PPPT. This realization has convinced some researchers that the value of PPPT over the years has been systematically underestimated (Jindal and Thase, 2003[17]). The persistence of mixed findings in the literature alerts the reader to the abiding uncertainty over the deployment of PPPT. The overall data nonetheless suggest that utilization of integrated approaches in MDD may be beneficial in selected cases.

Explaining PPPT: Potentiating Pathways

What might explain the reason that PPPT is often observed to be superior to monotherapy in clinical studies? A leading hypothesis is that, by modulating complementary brain regions, PPPT restores informational cross-talk between disrupted or depleted neurocircuits involved in mood regulation (Stahl *et al*., 2003[39]; Forgeard *et al*., 2011[9]). While both pharmacotherapy and psychotherapy have been shown by fMRI to normalize cortical activity in similar brain regions associated with symptom improvement, evidence suggests that the two modalities may differ in their proximal targets. Psychotherapy directly enhances prefrontal function and top-down cognitive-affective processing whereas pharmacotherapy appears to directly alter amygdala function and bottom-up, stimulus-driven limbic activation (DeRubeis *et al*., 2008[7]). Since normal mood regulation relies on reciprocal feedback and communication between prefrontal and limbic areas, the benefit of PPPT may lie in promoting neuroplastic changes that re-establish dynamic connectivity between these neuroanatomical structures (Crocker *et al*., 2013[4]). Although the precise mechanisms underlying neuroplasticity in PPPT specifically have yet to be elucidated, studies on ADT and on structured behavioural interventions (including intensive dialectical behaviour therapy for

borderline personality disorder) both suggest a role for altered gene expression and enhanced formation of neurotrophic factors (specifically BDNF and CREB) on the consolidation of adaptive neural pathways (Maletic *et al*., 2007[25]; Koch *et al*., 2009[21]; and Perroud *et al*., 2013[30]).

It is known that environmental factors such as positive and negative life stressors can set in motion epigenetic mechanisms that alter the strength of synaptic connections. Stressors experienced during childhood, for example, form memories by reinforcing a particular, well-defined, oft-triggered neural network. Potentiation of this network (i.e., memory consolidation) may affect the development of associated neuronal dendrites in a way that alters cognitive schemes and establishes mental representations that either are positive and resilient in nature or, conversely, may pose a risk for the development of future psychiatric symptoms (Gabbard, 2000[12]). Based on animal models, Kandel (1998[18]) provided evidence that learning induces new neural pathways and postulated that psychotherapy may cause similar changes in human brain synapses by providing patients with novel learning situations. More precisely, specific reinforcement of adaptive neural pathways fostered during structured psychotherapy sessions might modify or reconstruct maladaptive networks to facilitate a return to an undepressed phenotypic state. Although antidepressant agents were not used in Kandel's early models, there are substantial clinical data available today to suggest that ADT may also modulate and correct maladaptive neurocircuits to bring about symptom relief (Nestler, 2009[29]; Sweatt, 2009[40]; and Baxter *et al*., 1992[2]). This would suggest a synergistic mechanism through which either approach by itself, or combined as PPPT, may improve patients' endophenotypic function and relieve acute depressive symptoms. One way to conceptualize this mechanism is as follows: while ADT may help to increase the supply of "building materials" at each synapse by raising the levels of monoaminergic neurotransmitters in the brain during major acute episodes, psychotherapy may concurrently improve the neuroarchitectural "blueprint" by directing neurotransmission toward the consolidation of more adaptive neural pathways, thereby creating better, lasting connections needed to prevent remission (Forgeard *et al*., 2011[9]; Henn *et al*., 2002[15]).

Case Vignette

To illustrate when PPPT might be recommended in lieu of unimodal treatment, consider two hypothetical scenarios in which a young adult female patient presents to her psychiatrist with a 3-week history of unexplained sadness, anhedonia, low self-worth, excessive guilt, marked fatigue, and poor concentration. She is diagnosed with MDD, moderate, according to the DSM-5 criteria. Assume for simplicity, the absence of any suicidal ideation, pathologic personality, psychotic features, or other psychiatric or medical comorbidity.

In the first scenario, the patient doubts she will have time for regular psychotherapy, so she opts initially for single pharmacologic treatment with the SSRI, fluoxetine. In the second scenario, the patient has learned about some of the adverse effects associated with SSRIs, so she prefers instead to begin treatment with CBT. While success with monotherapy is certainly possible, it is easy to foresee how both strategies alone might fail to yield the desired long-term outcome of remission. For instance, in the first SSRI only case, if the patient lacks the cognitive schemata necessary for redirecting automatic, self-inflicting thoughts, or the positive coping mechanisms needed to handle the inherent psychosocial insults of school, work, or family obligations, she will be at an increased risk for relapse in the face of future life. The fact that fluoxetine may work to elevate her mood is important in the short-term but insufficiently protective in the long-run. Conversely, in the second CBT only case, if the patient experiences a pervasive, intractable, guilt-ridden, ruminative negative affect that persists throughout most of her CBT sessions, she will likely be hindered in her ability to learn and apply the CBT skills she is taught, no matter how well trained the therapist is. In other words, her recovery is stunted because it never has the chance to work robustly given the initial severity of the depression.

In both of the scenarios presented, PPPT is the next best step, the motivation for which is neurobiological as much as intuitive. As psychotherapy bolsters prefrontal function via structured learning and drug therapy targets limbic activity via increased availability of synaptic neurotransmitters, PPPT may lead to the normalization of dynamic neurologic connectivity between these interdependent brain regions, thus restoring healthy emotional-affective regulation. Theoretically, the SSRI may lessen some of the depressive symptoms so that CBT may more efficiently take place and facilitate further and long-lasting symptom reduction. This hypothesis is consistent with anecdotal reports that "medication can be helpful in diminishing the intensity of emotional and motivational symptoms in a way that allows more intentional cognitive strategies to be deployed effectively" (Crocker *et al*., 2013[4]). Lowering limbic hyperactivity may allow cortical hypoactivity to improve and then later re-instate its top-down dominance over limbic structures. In practice, it is up to the clinician to determine whether the added expense and effort of PPPT is warranted based on a thorough initial assessment of the patient's emotional, behavioural, and cognitive status.

Concluding Remarks [Figure 1]

Technological advancements in clinical research have accelerated the identification of pathways and mechanisms that have furthered our neurobiological understanding of MDD. In addition to the depletion of specific neurotransmitters and feedback dysfunction of the HPA axis, the

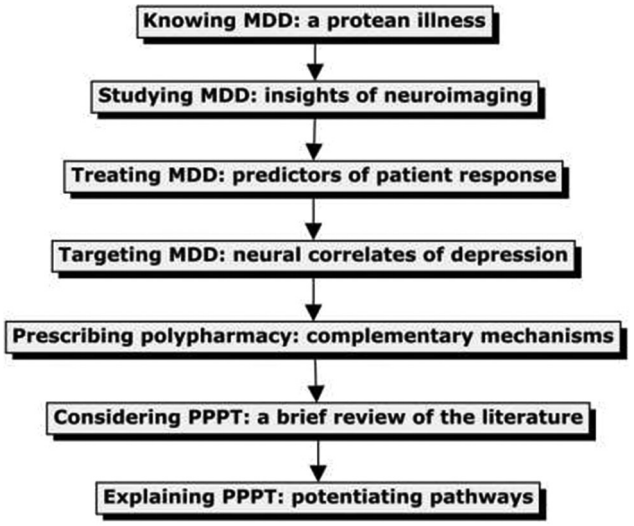

Figure 1: Flowchart of paper

pathogenesis of MDD appears to involve alterations in metabolism and cellular structure of well-defined brain regions, including the DLPFC, limbic system, and anterior insula. Functional neuroimaging may be used to document these neuroanatomic and neurofunctional changes and monitor endophenotypic responses associated with psychotherapy, pharmacotherapy, or both (PPPT).

This paper has sought to emphasize the need for personalized and, in selected cases, multimodal treatment, as dictated by the phenotypic heterogeneity and variance that exists not only among the MDD population but within the individual patient as well. All modalities likely affect and alter brain functioning in specific ways, the knowledge of which the clinician can use to his or her advantage. Different combinations of ADTs, for example, may modulate the levels of complementary neurotransmitters affecting one or more brain regions. Similarly, combining pharmacotherapy with different forms of psychotherapy (e.g., CBT, IPT) may offer the additive benefit of modulating gene expression and patterns of synapse formation in these same brain regions. In this way, PPPT may bring about an endophenotypic return to normal functioning by synergizing the formation of newly learned, adaptive neural pathways with increased levels of circulating neurotransmitters.

Trends in the literature suggest that PPPT may be especially useful among patients who are acutely or severely depressed, are at increased risk of relapse, or who frequently discontinue ADTs (Hollon *et al.*, 2014[16]; Friedman *et al.*,

2006[11]). However, history has seen an overwhelming majority of MDD trials that include mild-to-moderately symptomatic, noncomorbid patients as opposed to the severely afflicted.

More research is needed on the efficacy of MDD treatment in a more severely affected subgroup. Accordingly, more large-scale trials with adequate power to detect stratified differences may be required to determine how best to optimize MDD treatment.

Take Home Message

1. In contrast to the stigmatized view of MDD treatment as relying solely on trial-and-error, the selection of therapeutic options among ADT, psychotherapy, and PPPT should not be haphazard. Rather, it is consonant with, and rooted in, well-understood neurobiological principles
2. Neuroimaging has revealed how pharmacotherapy and psychotherapy improve the functioning of specific neural correlates of depression (e.g., DFPLC, insula, limbic system)
3. Ideally, in the future, information about a patient's endophenotype could be clinically integrated with other clinical data to specify treatment from which patients are most likely to benefit. This would become a form of personalized medicine that, combined with a pharmacogenomics approach, would enhance the care and likely the outcome on a patient-by-patient basis.

Conflict of interest

None declared.

Declaration

This is our original unpublished paper, not submitted for publication elsewhere.

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Questions that the Paper Raises

1. How does the heterogeneity of MDD presentation affect treatment selection?
2. What patient attributes influence MDD treatment response and efficacy?
3. What neuroanatomic/functional changes are associated with MDD treatment?
4. Can clinicians use neuroimaging data to better treat MDD patients?
5. Does combined treatment (PPPT) affect the MDD brain differently than monotherapy?
6. Does the efficacy of PPPT depend on a specific combination of therapies?

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Thomas L. Schwartz, MD, received his medical degree from and completed his residency in Adult Psychiatry at the State University of New York (SUNY) Upstate Medical University in Syracuse, New York, USA. Dr. Schwartz is currently Professor and Vice Chair of Psychiatry, and Director of Medical Student Psychiatric Education at SUNY Upstate Medical University. Active on many committees at SUNY, he also provides direct supervision, lectures in several courses, and directs and organizes continuing medical education events for the psychiatry department. Dr. Schwartz also maintains a private consultation practice.

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Dr. Schwartz has served as a principal investigator on many clinical trials. He is the editor of the textbooks: Depression: Treatment Strategies and Management, 2nd Edition and Integrating Psychotherapy and Psychopharmacology. He has most recently co-authored the text, Case Studies: Stahl's Essential Psychopharmacology: Volume 2.

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