Experience is a biochemical intervention: Reconceptualizing the "biologically based mental illness"

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Empirical evidence challenges the discriminant validity of the "biologically based mental illness" (BBMI) construct. Data indicate that interventions such as psychotherapy, placebo, and medication yield similar changes in brain function when effective. Drug and brain imaging studies show that psychological and biochemical phenomena can be manipulated reciprocally. Data suggest that mental disorders are biologically expressed, not epiphenomenal to a biological process. Suggestions are given for further research and alternative conceptualizations that may lead to changes in healthcare policy. (Bulletin of the Menninger Clinic, 69 [2], 157-171)

In recent decades, biopsychiatric research and treatments have increasingly supported Freud's (1914/1957) prophecy that "all our provisional ideas in psychology will presumably some day be based on an organic substructure" (p. 78). Yet, this shift in the biopsychiatric approach to mental disorders—from psychogenesis to biogenesis—obscures the mutual determinism of mind–brain relations. There is now clear evidence that the "organic substructure" can be targeted and changed through psychosocial interventions. For example, therapeutic psychological experiences alter brain function in ways that are analogous to psychopharmacological effects (Baxter et al., 1992; Brody et al., 2001; Goldapple, Segal, Garson, Bieling, Lau, & Mayberg, 2002; Hypericum Depression Trial Study Group, 2002; Martin, Martin, Rai, Richardson, & Royall, 2001; Mayberg et al., 2000; Mayberg et al., 2002; Penadés et al., 2002; Raleigh, McGuire, Brammer, & Yuwiler, 1984; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996).

Similarly, psychological states can be induced in normal humans and other primates so as to mimic the functional biology of pathological

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states (Kramer, 1993; Krüger, Goldapple, Kennedy, & Mayberg, 2002; Liotti, Mayberg, Brannan, McGinnis, Jerabek, & Fox, 2000; Mayberg et al., 1999; Pardo, Pardo, & Raichle, 1993; Raleigh et al., 1984). Recent treatment studies of depression and schizophrenia show increasing placebo efficacy, often yielding no significant difference between drug and placebo treatments (Ackerman & Greenland, 2002; Addington et al., 2002; Faries, Heiligenstein, Tollefson, & Potter, 2001; Fisher & Fisher, 1996; Hypericum Depression Trial Study Group, 2002; Kobak, Greist, Jefferson, & Katzelnick, 2002; Lima & Moncrieff, 2000; Mayberg et al., 2002; Moncrieff, Wessely, & Hardy, 2004; Peet & Horrobin, 2002; Quitkin, 1999; Taiminen et al., 1996; Walsh, Seidman, Sysko, & Gould, 2002). The complementary and interdependent nature of psychosocial and biochemical interventions on behavior and brain function has important implications for the diagnosis and treatment of mental disorders. If behavioral or experiential change is the goal of treatment, and both biological and ostensibly nonbiological methods yield such a change, then the discriminant validity of a "biologically based mental illness" (BBMI) construct (differentiated from nonbiologically based mental disorders or states) is threatened. Further, if biological and nonbiological interventions yield similar changes in brain activation, then third–party payment policies selectively favoring coverage for BBMI diagnoses (as in the case of mental health "parity" laws) may be untenable.

The hypothesis that biochemistry plays a mediating role rather than a causal role in psychological experience, and that this experience may be influenced through either "channel" (mind or brain) is at least several hundred years old (Foucault, 1988). This idea is supported by a convergence of evidence showing that a reduction of mental disorder symptomatology—whether following psychosocial treatment, placebo, or drug—corresponds to changes in brain function that are similar across different modes of treatment. Further, these biochemical changes appear to correlate more with clinical response than they do with mode of treatment. The bidirectional correspondence between mind and brain supports a "biochemical expression" construct more parsimoniously than a "biochemical basis" construct, and the choice to adopt either of these constructs establishes the groundwork for treatment decisions and policy.

It is unclear the degree to which psychopharmacological treatments affect the brain through a "direct" chemical action that is unrelated to expectancy and side effects. Mayberg et al. (2002) have hypothesized that different treatments, including placebo treatment, may affect a common circuitry through different initial sites of action; and Liotti et al. (2000) have hypothesized that normal and pathological mood states

involve shared activation patterns. For the purposes of research, treatment, and policy, a dualistic or polyistic mutual determinism model facilitates the testing of empirical and falsifiable hypotheses, and also guards against simplistic linear models of cause and effect that are currently used in the research of mental disorders.

Placebo studies

Placebos are increasingly effective

Recent studies comparing placebo with active medication have shown inconsistent results, yet there appears to be a greater similarity between drug and placebo for a variety of psychological maladies than previously reported (Faries et al., 2001). Researchers have shown inconsistent findings with regard to placebo response rates for different levels of baseline severity (Ackerman & Greenland, 2002; Gorenstein, Gentil, Melo, Lotufo–Neto, & Lauriano, 1998; Khan, Leventhal, Khan, & Brown, 2002; Kobak et al., 2002; Posternak, Zimmerman, Keitner, & Miller, 2002; Quitkin, Rabkin, Gerald, Davis, & Klein, 2000). Some authors have downplayed placebo effects at high levels of distress by attributing the placebo group's response to a regression toward the mean (Faries et al., 2001; Taiminen et al., 1996). Other authors have downplayed placebo effects at low levels of distress by attributing placebo efficacy to spontaneous remission (Posternak et al., 2002). Despite the lack of agreement about what factors may predispose research participants to respond to placebo, there does appear to be agreement about the trend toward increasing effectiveness of placebos overall.

Active drugs are effective for 40% to 60% of patients diagnosed with a variety of mental disorders, whereas placebos are effective for 20% to 65% of patients (Ackerman & Greenland, 2002; Kupfer & Frank, 2002; Quitkin, 1999; Quitkin et al., 2000). A number of recent studies have pointed to an increasing overlap between drugs and placebo. In a meta–analysis of 25 placebo–controlled clinical trials of drugs for obsessive–compulsive disorder (OCD), Ackerman and Greenland (2002) found that placebo response rates are rising in the literature. Walsh et al. (2002) found the same trend in a meta–analysis of major depression studies. The increase in placebo response and recent strategies developed to exclude placebo responders in biopsychiatric research raises concern about the degree to which drug action is pharmacological rather than the artifact of expectancy effects or methodological manipulation.

Response rates for placebo in the treatment of chronic schizophrenia vary between 20% and 50%, and can exceed response to active drug (Peet & Horrobin, 2002; Quitkin, 1999; Taiminen et al., 1996). For ex-

ample, in a study of treatment–resistant patients diagnosed with schizophrenia, Zhang, Zhou, Zhang, Wu, Su, & Cao (2001) obtained placebo response rates between 30.2% and 47.2%. These studies show that a moderate proportion of individuals diagnosed with chronic schizophrenia who are already taking optimized, stable doses of medication can improve to clinically significant degrees on placebo.

Recent research on other Axis I disorders, especially depression, yields greater placebo effects than those found in the treatment of chronic schizophrenia. A placebo–controlled 6–week study of sertraline for a major depressive episode in patients with remitted schizophrenia showed strong and equivalent treatment effects for drug and placebo groups (Addington et al., 2002) on several measures. For example, the placebo response rate was 48.1% and the sertraline response rate was 42.9% on the Calgary Depression Scale for Schizophrenia (CDSS).

A placebo–controlled 14–week study of fluoxetine for social phobia yielded a lack of significant difference between drug and placebo on the Leibowitz Social Anxiety Scale (LSAS). The fluoxetine group showed a 27.6% decline in LSAS score from baseline to endpoint; the placebo group's score declined 28.6%. On the Clinician Global Improvement (CGI) scale, 40% of the participants in the fluoxetine group were rated much or very much improved, compared to 30% of the placebo group (Kobak et al., 2002).

A multi–center study has demonstrated the equivalence, after 8 weeks, between placebo, herbal remedy (hypericum), and sertraline for major depressive disorder (Hypericum Depression Trial Study Group, 2002). Full response occurred in 31.9% of the placebo–treated patients versus 23.9% of the hypericum–treated patients and 24.8% of sertraline–treated patients. Fifty percent of the placebo group, 43.0% of the hypericum group, and 53.0% of the sertraline group had at least a partial response. Additionally, a continuation phase (to 26 weeks) was conducted. No relapses occurred for either the sertraline or the placebo group responders, and only one relapse for the hypericum group occurred.

In other recent research, placebo and fluoxetine were administered to two groups of hospitalized men with unipolar depression (Mayberg et al., 2002). Forty percent of the fluoxetine group and 57.1% of the placebo group responded to treatment. Moreover, responders to placebo showed regional metabolic changes in brain function that closely matched fluoxetine responders. Drug responders showed some additional areas of change in metabolism, and the magnitude of changes with drug treatment was generally greater, but these differences did not correspond with clinical differences. The authors hypothesized that

drug and nondrug treatments, including placebo, psychotherapy, or even spontaneous remission, may involve different initial sites of action within a common circuitry of activation.

Researchers at Eli Lilly and Company studying fluoxetine obtained placebo response rates of 41.8% and 50.0% at study endpoint in two studies (Faries et al., 2001). Kupfer and Frank (2002) reiterated the importance of including both placebos and active comparitors in studies comparing treatments, considering the variability of placebo and drug responses. Quitkin (1999) argued that by including both placebo and active comparitor, researchers can clarify whether a lack of difference or a low effect size are due to a negative study (comparitor treatment, but not target treatment, is different from placebo) or a failed study (comparitor treatment and target treatment are both indistinguishable from placebo). However, a failed study comparing medications and placebo may be a new kind of dodo bird study, where all psychiatric interventions have won, and "all must have prizes" (Luborsky, Singer, & Luborsky, 1975).

Methods affecting placebo response

A number of methodological controversies exist in the placebo–controlled research literature, including the use of active versus inert placebos to maintain double–blind conditions; and the use and length of a placebo "washout" (also called a "lead–in" or "run–in") period prior to randomization to treatment groups. The placebo washout technique is designed to identify and exclude participants who are placebo responders prior to the start of placebo–controlled studies. Faries et al. (2001) described this technique as a way to "establish or confirm diagnoses, obtain more reliable baseline scores, and confirm that safety entry criteria are met" (p. 561). However, these goals can be met without a placebo washout; and the biggest impact from this methodology is to eliminate placebo responders before randomization or comparison between groups, so as to reduce apparent treatment effects in the placebo group, and thus inflate the relative efficacy of the drug.

One of the effects of the washout technique, when successful, is to increase the gap between relative efficacy (the effect of a treatment in a controlled research trial) and relative effectiveness (the effect of a treatment under real–world conditions). Individuals who obtain prescriptions for psychotropic drugs are not first screened for their response to placebo. The extent to which their clinical response may be due to placebo effects is underestimated by the washout methodology.

Longer single–blind prerandomization washouts have been associated with less improvement on placebo and several drugs for obsessive–compulsive disorder (Ackerman & Greenland, 2002). On the

other hand, several studies have shown that single–blind placebo washouts during prerandomization are not particularly effective, in comparison with no washout (Faries et al., 2001; Greenberg, Fisher, & Riter, 1995). Recently, Faries et al. developed an improved placebo washout technique called a "double–blind variable placebo lead–in period." They kept experimenters blind during the prerandomization washout phase, and defined placebo–response disqualification as a greater than 25% decrease in Hamilton depression (HAM–D) score during the washout. All participants were then randomized and continued through the remainder of the study under double–blind conditions (disqualified participant data were later excluded from the main analysis). They found, as later replicated by the Hypericum Depression Trial Study Group (2002), that placebo washout responders maintained their response at study endpoint. The double–blind washout technique was more successful than a single–blind washout at identifying placebo responders for exclusion from the data set, thus amplifying the differences between drug and placebo groups at study endpoint. Faries et al. concluded that this technique was effective at reducing the postrandomization placebo response. However, it did not reduce the placebo response per se; it disqualified more placebo responders from analysis.

Another controversy in placebo research relates to the use of active versus inert placebos and the blindness of drug trials in general (see Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994, for a review). The double–blind prerandomization placebo washout procedure provides support for the idea that in placebo–controlled studies, experimenter blindness from prerandomization through study completion affects outcome: experimenter blindness increases the prerandomization placebo response rate, excluding more placebo responders from analysis, and accentuating drug–placebo differences (Faries et al., 2001). Greenberg et al. have argued for the importance of "blinder" conditions through the inclusion of active placebos or comparitor drugs, finding that as blindness increases, antidepressants show less of an effect in comparison to placebos. Also, Lima and Moncrieff (2000) found evidence suggesting that as drug side effects increase in the drug group, placebo response decreases in the placebo group. This may be due to an inadvertent unblinding of experimenters or participants and needs to be studied prospectively.

Quitkin (1999) argued that studies showing active placebos leading to a greater clinical response were flawed by methodological problems endemic to such studies in the early 1960s: that antidepressant doses were inadequate, and study lengths were sometimes quite short (4 weeks or fewer). Quitkin et al. (2000) argued that the reason clinicians

are often able to correctly guess which participants received the active drug is due to the greater clinical response in those participants, not to the blind being broken by drug side effects. This hypothesis is not supported by a recent inert placebo study by the Hypericum Depression Trial Study Group (2002). This study was 8 weeks in length, dropout rates between drug and placebo groups were equivalent at 8 weeks and throughout a 26–week continuation, and flexible dosages of sertraline were allowed, based on clinical response in this moderately depressed group. Sertraline had substantially and significantly higher rates of side effects than placebo. As in previous studies, clinicians' proportion of correct guesses (66%) about which participants received sertraline greatly exceeded the chance proportion of approximately 33%, and this was not the case for hypericum (29%) or placebo (36%). Nevertheless, clinical change as measured by the HAM–D did not differ across groups; and participants who guessed correctly did not show a different clinical response on the HAM–D than those who guessed incorrectly. Side effects, not clinical response, appeared to be responsible for correct guesses of drug versus placebo by clinicians and participants.

These recent studies demonstrating substantial placebo effects for mental disorders indicate that placebo administration is effective and sometimes equivalent to established medications. A possible reason for such strong placebo effects is that side effects from newer medications are often less noticeable than from older medications. With fewer cues as to which group a participant has been assigned, placebo effects may increase. Nevertheless, experimenters and participants still may not be adequately blind without the use of active placebos: they are able to distinguish which treatment group participants are in at greater–than–chance levels. With a better blind, greater placebo response may necessitate more rigorous responder washout procedures to eliminate this effect. Yet, placebo response, far from hindering our understanding of mental disorders, treatments, and mechanisms of action, indicates that clinical changes that result from drug action may also be susceptible to other modes of action that indirectly affect biochemistry and brain function through psychosocial processes.

Brain–imaging studies

Patients diagnosed with mental disorders

Studies comparing pre– and posttreatment brain function show that biochemical and psychosocial interventions lead to similar biochemical changes in treatment responders. The construct of a BBMI presumes a directional, causal relationship between biochemical function and behavior, or that biological process is the foundation of mental disorders.

Current research does not support such a view. On the one hand, placebo studies suggest that in many instances, medications may exert effects on behavior at a psychosocial (expectancy) level rather than a biochemical level. On the other hand, brain–imaging studies indicate that psychosocial interventions affect biochemistry. These studies in particular show that the biology of mental disorders is a level of expression, not the basis, of psychological problems. The functional biology of the brain can be treated "directly" through pharmacological agents, but also through other means that affect this biology.

A number of positron emission tomography (PET) studies converge on the mutual determinism of brain function and psychosocial experience. In a study of depression, Mayberg et al. (2002) showed mostly equivalent changes in regional brain metabolism in responders to both fluoxetine and placebo. When participants became substantially less depressed, their brain activation changed in similar ways, regardless of whether they had received an inert pill or an active compound.

In another PET study, Brody et al. (2001) showed that participants with major depressive disorder who received either paroxetine or interpersonal psychotherapy showed equivalent changes in regional brain metabolism. Goldapple et al. (2002) also found brain changes that appeared to mediate clinical response to cognitive–behavioral therapy for unmedicated depressed patients. They postulated a normalization of pretreatment abnormalities in prefrontal, parietal, and mid–cingulate (limbic) areas toward levels seen in normal controls.

In a 6–week, single–photon emission computed tomography (SPECT) study, Martin et al. (2001) pointed out that the 6–week duration may not have been long enough for the interpersonal psychotherapy treatment to reach an effective dose. Nevertheless, participants treated with interpersonal psychotherapy showed some equivalent regional metabolic changes to participants treated with venlafaxine hydrochloride.

Two PET–imaging studies before and after successful treatment of obsessive–compulsive disorder (OCD) confirm that psychosocial interventions, like chemical interventions, can modify brain function when they are effective, adding support for the hypothesis that clinical change predicts comparable brain function changes regardless of the mode of treatment.

Baxter et al. (1992) found that after 10 weeks of treatment, glucose metabolism in the caudate nucleus of OCD patients responsive to behavior therapy changed to the same extent as caudate metabolism in patients responsive to fluoxetine. Nonresponders in both the fluoxetine and behavior therapy groups showed no such change in metabolic rate. In a replication of Baxter et al.'s study, Schwartz et al. (1996) found that after 8 to 12 weeks of behavior therapy, medication–free participants with OCD who responded to behavior therapy had a significant bilateral re-

duction in caudate glucose metabolism also that was significantly greater than for poor responders to the treatment. These brain–imaging studies provide converging evidence with placebo studies, supporting the view that although a mental disorder is expressed physiologically, this does not imply that a pharmacological intervention must be used to change this physiological expression. Further, changes in brain function following drug administration may be more a function of concomitant clinical change than a function of the pharmacological properties of the drug under investigation: drug *responders* rather than drug *recipients* tend to show brain function changes that are comparable to responders to psychosocial interventions such as psychotherapy or placebo.

One strategy for determining whether pharmacological action early in treatment is responsible for later clinical response is to measure early changes in brain function after starting drug treatment. A study using this methodology did not show support for these changes. Cook et al. (2002) found evidence suggestive of equivalent brain function within 1 week of placebo or drug administration for those participants who clinically responded to either condition after 8 weeks. Additionally, Mayberg et al. (2000) found no difference in brain activation patterns after 1 week of fluoxetine treatment between endpoint drug responders and nonresponders. After 6 weeks of drug treatment, however, both clinical response and brain function differences emerged. The results of these two studies suggest that brain function changes correspond to treatment response, not pharmacological action. Adding support to this hypothesis is Mayberg's (2002) comparison of drug and placebo responders and nonresponders. The placebo group and drug group showed similar brain function changes after 6 weeks of treatment. Further, Mayberg et al. (2000, 2002), Baxter et al. (1992), and Schwartz et al. (1996) found that only those drug–group participants who showed psychological change also showed change in their brain function. Clinical improvement in patients diagnosed with BBMIs correlates with brain function change, without providing clear evidence for the role and timing of pharmacological effects in the change process. Since non–biochemical interventions such as placebo and psychotherapy similarly lead to brain function changes when the interventions are effective, it appears that brain function change in the case of mental disorders is as likely to be epiphenomenal to clinical (behavioral or experiential) change as it is to biochemical change, and perhaps more so.

Mood induction in normal volunteers

Brain–imaging studies of normal volunteers provide evidence for the nondiscriminability of the BBMI construct. In a PET–imaging study of brain function during transient mood changes, Pardo et al. (1993) ma-

nipulated consistent brain changes in normal volunteers. Participants were asked to access their sadness (average rating of 8 on a 10–point scale) by thinking about personal losses. The authors summarized that their "data suggest that inferior and orbitofrontal activation may relate to 'on–line' experiential aspects of self–induced dysphoria" (p. 716). Pardo et al. emphasized that neuroimaging studies that show a difference between psychiatric patients and normal controls do not necessarily show pathophysiology per se, but rather the physiology of the here–and–now experiential process. The implication of this study is that physiological markers may be an effect, not merely a cause, of psychological experiences.

Liotti et al. (2000) confirmed the finding by Pardo et al. (1993) by invoking sadness and anxiety in two groups of normal volunteers. They found disparate activation patterns between these two psychological states, but that there is a "shared circuitry or common pathway [that] exists between normal and pathologic forms of sad mood and anxiety that may be vulnerable in a disease state" (p. 40). Mayberg et al. (1999) found that induced transient sadness in normal volunteers in one group and recovery from depression (whether through placebo or fluoxetine response) in another group were characterized by "reciprocal changes involving nearly identical limbic–paralimbic and neocortical regions with both acute and chronic changes in negative mood state" (pp. 678–679). While such overlaps in brain function are not always exact between induced moods in normal volunteers and more long–lasting or severe clinical states (e.g., Krüger et al., 2002), there is clear evidence that clinical syndromes such as depression and anxiety disorders (which are considered to be BBMIs) involve pathways and mechanisms similar, and possibly identical, to those of "normal" negatively charged affective states.

Converging evidence from normal volunteers and clinical populations, and with a range of clinical syndromes, shows that experiences lead to predictable, consistent biochemical changes in the brain, whether these experiences are induced through direct chemical interventions (drug) or psychosocial interventions (placebo, experimental induction, or psychotherapy). Brain–imaging technology has provided a means to examine directionality between brain function and clinical state. Research evidence, to date, supports a "biological expression of mental phenomena" construct, not that particular mental disorders are biologically based.

Research directions for biochemical and psychosocial complementarity

Research conducted over the past two decades has increasingly pointed to a solution to the mind–body problem that returns to an an-

tiquated position. It appears that there is some support for Foucault's (1988) history of 18th century European thought on mind–brain relations:

The soul and the body are in a perpetual metaphorical relation in which qualities have no need to be communicated because they are already common to both; and in which phenomena of expression are not causes, quite simply because soul and body are always each other's immediate expression. . . . If it is true that there exists a realm, in the relations of soul and body, where cause and effect, determinism and expression still intersect in a web so dense that they actually form only one and the same movement which cannot be dissociated except after the fact; if it is true that . . . there are qualitative, as yet unshared kinds of a priori which subsequently impose the same values on the organic and on the spiritual, then we see that there can be diseases such as madness which are from the start diseases of the body and of the soul, maladies in which the affection of the brain is of the same quality, of the same origin, of the same nature, finally, as the affection of the soul. (p. 88)

This shift in conceptualizing mental disorders yields a number of difficulties. Given a unity between brain and mind (i.e., that changes in one of these channels of expression tautologically changes the other), a differentiation between biologically based and non–biologically–based mental disorders is not empirically supported. And further, the idea that what sets mentally ill persons apart from non–mentally ill persons is a "chemical imbalance" or biological problem of the brain reduces to a strategy for treatment rather than being an ontological argument supported by empirical research.

Current debates between guilds about mental health policy often display a tension between the "no–fault" biological manifestations of illness (treatable by medication and supportive counseling) on the one hand, and the existential responsibility for one's capacity to change (treatable by psychotherapy and other experiential methods) on the other. Many clinicians have called for an integration of the split between the two treatment approaches of medication and psychotherapy by combining the two; yet this development may derive less from a coherent empirical or theoretical approach to mental disorder than from a selective interpretation of the literature or a pragmatic appeal to economic pressures. It is imperative that psychologists and psychiatrists understand the mutuality between psychosocial and biochemical processes so as not to abdicate treatment decisions and strategies for BBMIs to those who employ biologically based treatments. With-

out this understanding, the erosion of psychosocial treatments for emotional disorders is likely to continue as more psychological maladies are characterized in terms of the biochemical processes that mediate them.

Further research is needed to prospectively study and clarify the bidirectionality of changes in mental function and brain function in people diagnosed with a wider variety of mental disorders, and in normal volunteers. Directions for future brain–imaging research include: determining under what conditions and to what extent responders to biochemical and psychosocial treatments exhibit similar changes in brain function across modes of treatment; confirming whether treatment type or treatment response better predicts changes in brain function; and studying induced psychological experiences in normal volunteers to determine to what extent such "normal" states are distinguishable from clinically significant states.

Placebo–controlled drug trials have demonstrated that the use of placebo conditions is ethical: in many cases of clinically significant mental disorders, placebos exert moderate to strong treatment effects in comparison to active drugs. Because of the increasing number of studies showing such results, placebo–controlled studies clearly are necessary; and the development and use of active placebos with side–effect profiles mirroring their active drug counterparts is indicated. Researching these areas will further elucidate the interdependent relationship between mental experiences and brain processes, which—while blurring the distinction between pathology and wellness—may yield greater knowledge about the extent to which we can move between these two states of being.

Clearly, all psychological problems are biochemically expressed because the brain is what mediates our experience. Any treatment, when effective in changing one's experience, must also be biochemically expressed. Current evidence indicates that the BBMI construct does not have discriminant validity; and biochemical treatments do not appear to have a unique advantage in changing the biochemical expression of psychological maladies. Further research in this area may improve service to patients by providing epistemological balance, a choice of treatment modality payable by insurers, and a reasonable degree of causal complexity appropriate to the subjects of clinical psychology and psychiatry.

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