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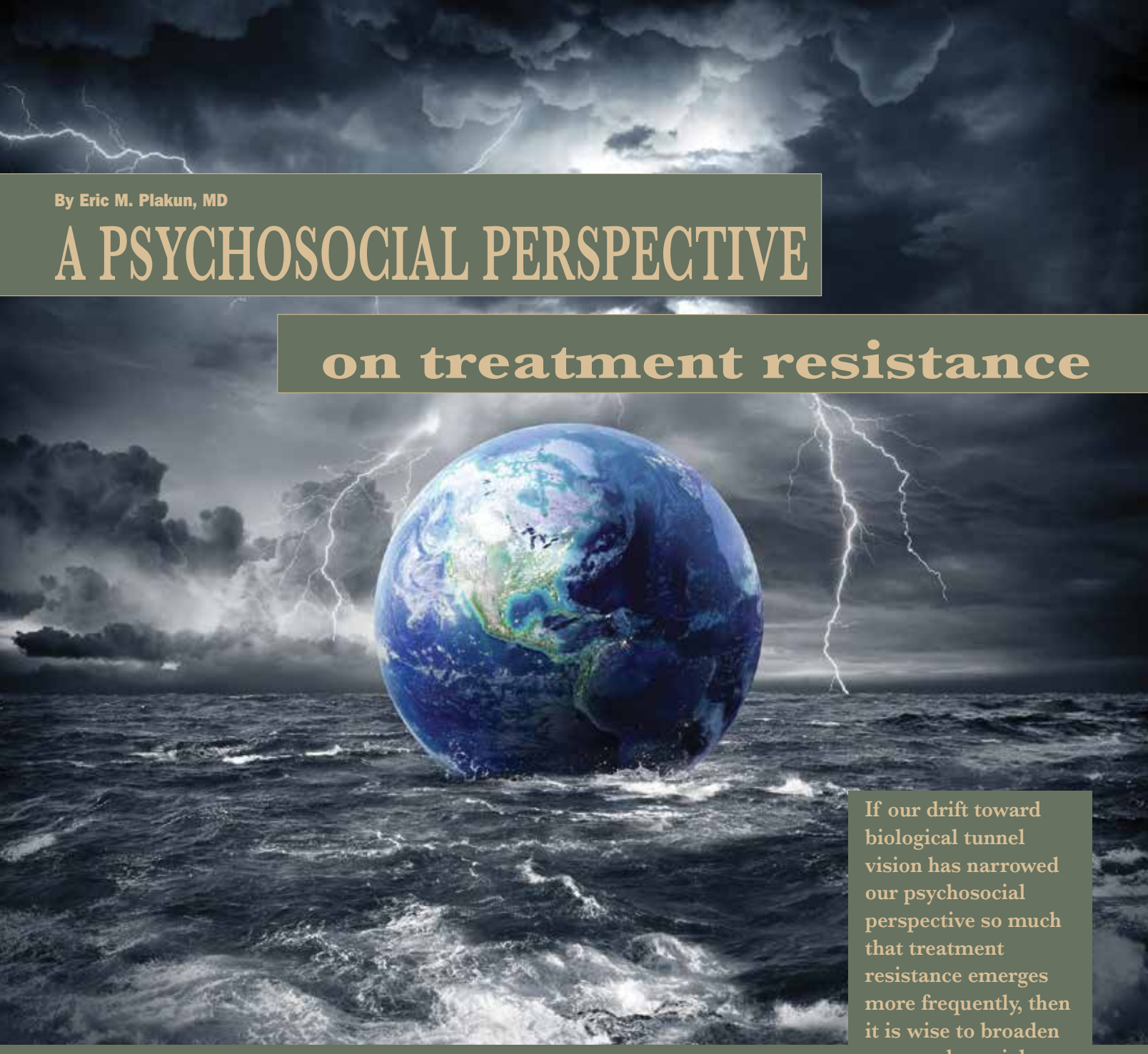
A PSYCHOSOCIAL PERSPECTIVE on treatment resistance



If our drift toward biological tunnel vision has narrowed our psychosocial perspective so much that treatment resistance emerges more frequently, then it is wise to broaden our psychosocial approach to patients.

Despite advances in research methodology and efforts in the mental health and addictions fields to move toward evidence based treatment, large numbers of patients fail to respond to our best evidence based treatments. This has led to growing recognition of the phenomenon of treatment resistance. For example, during recent 20-year period overall Medline citations in psychiatry increased 25%, while citations on treatment resistance increased 800% (Mintz & Belnap, 2011).

Although there is no universal definition of treatment resistance, as used here and in much of the field it refers to failure to respond adequately to at least two evidence based treatments to which a patient has adhered. The problem of treatment resistance is related to the complexity of mental health and substance use disorders, but also to the drift toward a biologically reductionistic stance that takes a narrow, unimodal view of mental disorders. For example, most algorithms for treatment of depression offer a rational sequence of steps for choosing medications, with little or no attention to psychosocial factors and how they may be part of the causation and treatment of this mood disorder. It is my contention that the drift toward biological tunnel vision is based in large part on widespread and sometimes unwitting belief in three false assumptions about mental disorders that emerging science suggests are untrue (Plakun, 2015).

Three False Assumptions

These include that (a) genes = disease; (b) patients present with single disorders that respond to evidence based treatments; and (c) the best treatments are pills. Let's look at these one at a time.

Genes = Disease: With the decoding of the human genome in 2003, there was hope that the genetic underpinnings of mental disorders would be unearthed. However, genetic research has not identified genes underlying mental disorders like schizophrenia, depression, or bipolar, anxiety or substance use disorders. Using sample sizes large enough to find relevant single nucleotide polymorphisms (SNPs) for diabetes, inflammatory bowel disease and some cancers, searches for SNPs associated with mental disorders have led either to no clear genetic loci, as in depression, or to so many candidate SNPs, as in schizophrenia, that it is clear inheritance is not a matter of straightforward Mendelian genetics. Although it is clear mental disorders are heritable, the mechanism of inheritance is much more complex than suspected.

Caspi and colleagues' seminal study (2003) of short and long alleles of the serotonin transporter promoter gene, the most cited paper of the first decade of this century, opened the eyes of mental health clinicians to gene-by-environment interactions, or epigenetics. In Caspi's now replicated study homozygous short alleles of this gene were associated with greater risk of adolescent or adult depression in those children who were exposed to early adverse experiences like abuse than those with homozygous long alleles. This finding helped shift thinking toward a notion of genes conferring vulnerability to environmental factors, like early adversity. Of note, though, this "genes = vulnerability" model also falls short of fitting the data.

As it turns out, those with homozygous short alleles also have the least likelihood of depression in the absence of early adversity—a lower risk than those with homozygous long alleles. This important finding is often overlooked in ways that reflect our bias toward a stress-diathesis "vulnerability" model of disease (Plakun, 2016). The actual data are less consistent with a model of epigenetic vulnerability and more consistent with a model of epigenetic "plasticity," where genes respond to beneficial and adverse environments with differential susceptibility (Belsky, 2009). If we can open our minds to follow the data and think this way, we may learn much about what leads to disease and to resilience.

The shift from a genes = disease model to a gene-by-environment or epigenetic model follows recognition that environmental factors are far more important in how genes work than we suspected.

Concurrently, the so far unsuccessful search for biomarkers of mental disorders has been likened to a quest for the Holy Grail, while early adverse experiences have emerged as powerful predictors of later psychiatric, substance use and medical disorders. In the absence of biomarkers, early adversity appears to be an "enviro-marker" (Molnar, Buka, & Kessler, 2001).

Further demonstrating the power of environmental versus genetic factors in mental disorders, depressed mothers tend to have adolescent children with depression whether the children are biologically related or adopted (Tully et al., 2008), while a study of mothers who were twins suggests that anxious mothers transmit anxiety to their children principally in non-genetic ways (Eley et al., 2015).

Patients present with single disorders that respond to evidence based treatments: Studies of major depression show that 15 to 50% of patients fail treatment (Thase et al., 2007), with comparably high failure rates for other disorders. The large, multi-site STAR*D study of depression teaches us not only about the frequency of treatment failure in depression, but also about what kind of depressed patients present for treatment. Surveying the STAR*D sample, Wisniewski et al. (2009) report that fully 78% of the sample presented with the kind of comorbidity or suicidal ideation that would exclude them from most randomized controlled trials of medications or other treatments. This comorbid majority had lower response and remission rates to medications. This validates the experience of many clinicians that their depressed patients seem sicker than those who respond to drugs developed and tested in carefully screened non-comorbid samples.

Hence, comorbidity, along with early adversity, emerges as a significant contributor to treatment resistance. More specifically, the Collaborative Longitudinal Personality Disorder or CLPS study demonstrates that comorbid personality disorders, especially comorbid borderline personality disorder (BPD), "robustly predicts the persistence of major depression" (Skodol, 2011). Skodol and colleagues propose that diagnosis and treatment of personality disorders is essential in treating major depression. According to the practice guideline for treatment of personality disorders, psychotherapy, not medication, is the mainstay of treatment. However, using DSM-IV, the mostly frequently diagnosed Axis II disorder was "Deferred," suggesting that clinicians often fail to attend to personality disorders and to their robust contribution to treatment resistance.

Our learning from depression teaches us that most depressed patients present with comorbid disorders—including undiagnosed personality disorders—and that these comorbid patients are harder to treat, while we often fail to diagnose and treat personality disorders as part of the treatment of depression.

The best treatments are pills: We are learning that we have overestimated the efficacy of medications by as much as a third when unpublished studies that did not show advantage to an antidepressant drug over placebo are included in data analyses (Turner et al., 2008), and that as much as 75% of antidepressant efficacy is due to the placebo effect (Kirsch et al., 2008). This high placebo response rate likely relates to the concerned and caring relationships that are part of the placebo arm of a randomized trial. Meanwhile, thousands of studies have demonstrated the efficacy of cognitive behavioral therapy (CBT) and hundreds have demonstrated

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the efficacy of psychodynamic therapy. We tend to be blind to the power of psychosocial factors in treatment, but the data should open our eyes.

What Works With These Patients?

Nemeroff and colleagues (2003) compared nefazodone and a form of CBT called Cognitive Behavioral Analysis System of Psychotherapy (CBASP) in treatment of 681 patients with chronic major depression, many of whom had early abuse histories. They report that in patients with abuse histories, chronic depression responded better to psychotherapy alone than to medication alone, while the combination was only slightly better than psychotherapy alone. They conclude that, in patients with depression and histories of abuse, psychotherapy may be an essential component of treatment.

Recent studies report the efficacy of CBT (Wiles et al., 2016) and long-term psychodynamic therapy (Fonagy, 2015) in patients with previously treatment resistant depression. The response of treatment resistant disorders to psychotherapy is not surprising since early adversity and comorbidity, especially personality disorder comorbidity, make substantial contributions to treatment resistance. Given the evidence, we are wise to look beyond biology in treating patients with treatment resistant depression and other comorbid disorders.

Where is the "Resistance" in Treatment Resistance?

Given the complexity of what it means to be human, there has been resistance to treatment as long as there has been treatment. Some patients resist treatment because they don't want it for reasons of their own, rational or otherwise. They don't see it as offering something they need or want. Other patients seem caught in the ambivalence that is part of being human and are resistant because they fail to adhere to medication or therapy regimens even when they have sought them. In these instances the resistance may be located in the patient. However, for patients who have lived lives of profound early adversity, in which they have experienced abuse, neglect, abandonment, deprivation or the like in early relationships with authorities like parents or others, failing in treatment may represent a less than trusting response to authority figures like doctors.

Further, in a treatment system that often leaves such people powerless and passive recipients of treatment doled out by authorities, failing treatment may be the best way for them to find their voice, empowerment and agency in a life of being controlled, defeated and rendered passive. In these instances, again, treatment resistance may be located in the patient. However, I would propose that much of the resistance in treatment resistance is located in our unimodal, biologically reductionistic treatment models and in our prejudices about treatment, and thus in ourselves and in our treatments, and not in our patients (Plakun, 2011).

Toward a Psychosocially Informed View of Treatment Resistance

If our drift toward biological tunnel vision has narrowed our psychosocial perspective so much that treatment resistance emerges more frequently, then it is wise to broaden our psychosocial approach to patients. In my experience, it is a psychodynamic perspective that allows the most useful integration of psychosocial approaches into our treatments. One example of such an integration is "psychodynamic psychopharmacology" (Mintz & Belnap, 2011), which is an approach to prescribing that attends to the meaning effects of medications, not just to their biochemical effects, and to "how" to prescribe in addition to "what" to prescribe. Mintz and Belnap (2011) speak about treatment resistance "to" medications, "from" medications and about the "nocebo" effect.

The nocebo effect is a negative placebo effect in which, instead of an expectation of benefit from treatment, patients with histories of early adversity have an expectation of harm that detracts from the effectiveness of medications. Patients who are nocebo responders often report intolerable side effects even to miniscule doses of drugs.

Treatment resistance from medications may take the form of overprescribing when the psychiatrist's zealous wish to be helpful leads to over sedation. A good example of treatment resistance to medications that is based on meaning is a patient I recall. She was a psychotically depressed mother whose child had died, for whom neuroleptics and antidepressants did not reduce auditory hallucinations—until it was recognized that the hallucinated voice was that of her dead child. To respond to the medications would mean she had lost her daughter forever. This mother could respond to medications only after this was grasped and the work of grieving was undertaken in her psychotherapy.

There are other things we can do to be more responsive to the psychosocial needs of our patients. A psychodynamic focus that offers a nuanced, complex, but integrated systems perspective on work with treatment resistant patients offers much promise. Here are a few recommendations for improving our psychosocial focus, many of which are fundamentals of a psychodynamic approach:

- Consider personality disorder diagnosis in every patient.
- Get the patient's developmental and narrative history, looking for therapeutic stories about early adversity that are being repeated in the present that may help explain what underlies treatment resistance and how it may even make sense in a life of abuse, neglect and deprivation.
- Negotiate a therapeutic alliance that respects both the freedom and the responsibility of patients as active agents in their treatment. After all, we have learned that nothing has a more powerful treatment effect than a strong therapeutic alliance, and it cannot be strong or even an alliance unless a patient's freedom and responsibility are part of it.
- Focus less on symptom suppression than on helping people take charge of their lives. What would make their life more livable? What are their goals? What is in the way of achieving them?
- Use treatment relationships that continue over time, that attend to the meaning of symptoms and to the meaning of treatment resistance itself, and that respect the voice of the patient.

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- Learn to tolerate the despair and hatred that are often part of the experience of patients who have experienced early adversity. They have learned early that life is not fair, that those they depend on may fail, injure or abandon them. These experiences will tend to repeat in the course of treatment as we, as imperfect humans, fail them in ways large or small. In psychoanalysis this stance is known as being able to tolerate the negative transference, i.e., tolerating being hated or experienced as a corrupt authority at times as therapy goes through cycles of rupture and repair over time. We are wise to avoid "refusing" these transferences. Therapists are ultimately imperfect humans who are capable of unwittingly injuring patients. We must avoid retaliating for anger by counterattacking or by ending the work. Learning to negotiate a viable relationship that can weather storms of hate and anger may well be of use to patients—as they have come by their anger and sense of disappointment quite honestly.

- We are wise to understand that enactments are part of work with such patients (Kayatekin & Plakun, 2011). Enactments are enmeshed tangles we may get into with patients in which we and they get caught in mutual and complementary projective identification involving issues from the lives of both participants. If we can detect, then analyze and then utilize what we have learned in these enactments, we can deepen the work. However, doing this often requires an outside perspective, a "third" who can consult to us about what we have gotten caught in. Enactments are a slippery slope. However, as in skiing, the practice is meant to take place on a slippery slope. In skiing as in therapy, the trick is to find one's edges while sliding down the slippery slope, staying in control and understanding the dynamics of the slide.

- Develop and use treatment teams that (a) integrate treatment by all providers; (b) include treatment for comorbid disorders; (c) use a psychodynamic formulation to guide the work; (d) detect, analyze and utilize learning from enactments; and (e) that view splits and disagreements on the team as opportunities to understand the splits and struggles of the patient's inner world and perceived family experience.

With inclusion of psychosocial approaches like these we can better attend to aspects of patients' life contexts that are relevant to helping them emerge from suffering and from treatment resistance.

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