How (Not What) to Prescribe: Nonpharmacologic Aspects of Psychopharmacology

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KEYWORDS

• Depression • Psychopharmacology • Treatment resistance
• Doctor-patient relationship • Alliance • Treatment outcome

Over the past 2 decades psychiatry has benefited from an increasingly evidence-based perspective and a proliferation of safer and more tolerable antidepressant treatments. Despite these advances, however, there is no evidence that treatment outcomes are better than they were a quarter of a century ago. New psychiatric medications come on the market every year, often with great enthusiasm, only to be tempered by the realities of clinical practice. More recently, it seems that novel antidepressants have not even been able to generate much fanfare. This phenomenon is not particularly surprising considering that the widely publicized STAR*D trial[1,2] reported relatively underwhelming performances of various psychopharmacologic agents when applied in real-world settings. One possible explanation for the failed promise of psychopharmacology rests in the fact that the field has been so enthusiastic about biological treatments that psychosocial aspects of psychopharmacology have been almost entirely neglected in recent years.

There is a growing body of evidence that suggests that nonpharmacologic or nonspecific factors in psychopharmacology are at least as potent as the putative active ingredients in the medication. Metaanalyses reviewing US Food and Drug Administration databases (which include a relatively unbiased sample of both published and unpublished data from antidepressant clinical trials) suggest that 75% to 81% of drug response can be attributed to nonpharmacologic effects, such as placebo.[3–5] Other research from well-designed placebo-controlled trials show that a strong pharmacotherapeutic alliance is an even more powerful antidepressant than the actual drugs that are prescribed.[6]

McKay and colleagues,[7] in their groundbreaking analysis of outcome data from the Treatment of Depression Collaborative Research Program, an extensive, National Institute of Mental Health–funded multicenter placebo-controlled trial of the treatment

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of depression found a provocative prescriber effect. They were able to stratify outcomes by prescriber, despite the fact that experimental conditions tightly controlled most aspects of the doctor-patient engagement. One-third of the psychiatrists in the study could be described as highly effective, achieving superior results with active drug. Another one-third of prescribers exhibited average performance, and another one-third were relatively ineffective. More striking perhaps is the fact that the most effective one-third of prescribers achieved better outcomes with placebos than the least effective one-third of prescribers got with active antidepressants. This result suggests that *how* the doctor prescribes is even more important that *what* the doctor prescribes.

Whereas there is overwhelming evidence identifying the contributions from nonpharmacologic factors in drug response, forces inside and outside of organized psychiatry have tended to promote a model of treatment that tends toward biological reductionism.[8–10] These forces include optimism about neuroscientific advances as well as the domination of managed care and its promotion of a model that incentivizes simplified and split treatments promising short-term cost savings. It is perhaps telling that, of 26 English language studies in the past 2 decades exploring interventions to promote antidepressant adherence, 25 of those studies came from primary care departments and only one came from organized psychiatry.[11]

This article is an effort to provide some balance and offer some guidance to psychiatric prescribers about how to prescribe in order to promote better treatment outcomes. Where possible, the authors cite evidence pertaining directly to the literature on the treatment of depression. In some cases, recommendations are extrapolated from findings with other psychiatric conditions. It is likely, given the seeming universality of nonspecific factors in healing, that the recommendations made here pertain to the range of psychiatric conditions and not just depression.

THE PROBLEM OF TREATMENT RESISTANCE

As our awareness of the limitations of medications grows, so too does awareness of the problem of treatment resistance. Over the past 3 decades, references to treatment resistance in the psychiatric literature have outpaced the total number of references by a factor of 16.[8] STAR*D and other studies[12–14] suggest that a minority of patients with depression will fully recover with pharmacologic treatment. The mainstream media have begun to reflect the growing disenchantment with psychopharmacology with skeptical articles about antidepressants appearing in a wide variety of major news outlets in the last several years. Without a transformative shift in our approach to depression, the field may unwittingly move from the era of psychopharmacology and into an era of treatment resistance.

THE MEANING OF MEDICATION

Nonpharmacologic factors contributing to patient response in medication trials are well-established, although these findings are often sequestered in the psychology literature. In their comprehensive review of the placebo response, Fisher and Greenberg[15] lay out a compelling body of evidence examining the nonpharmacologic aspects of drug response. Factors ranging from the color[15–17] or expense[18] of the pill to the route of administration,[19] the setting in which the pill is administered,[15] and the attitude of the prescriber[15,20] all seem to influence outcome (**Table 1**). Similarly, mounting evidence suggests that the prescribing process equals or exceeds the clinical import of the putative active ingredient of the antidepressant. However, our field is only beginning to understand what the most effective prescribers do. As

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Table 1
Medication characteristics affecting treatment outcome

Medication Characteristics	Evidence
Color	de Craen et al,[17] 1996
	Fisher & Greenberg,[15] 1997
Expense	Waber et al,[18] 2008
Setting of Administration	Fisher & Greenberg,[15] 1997
Route of Administration	de Craen et al,[19] 2000

interpersonal processes cannot be patented, psychopharmacology process research has unfortunately received only a miniscule fraction of the investment that has been made into researching the effectiveness of specific drugs. Such process research, central to the study of the psychotherapies, is much needed if the field of psychiatry is truly committed to improving treatment outcomes in pharmacotherapy.

The impact of the physical characteristics of the medication, the symbolic aspect of taking (or refusing) a medicine, and the interpersonal relationship tied to a medication (eg, pill as substitute contact with the doctor) can be integrated into a phenomenon called meaning effects. Despite the considerable evidence suggesting these meaning effects are central to medication response, there is no widely accepted method for incorporating them into clinical practice. Psychodynamic psychopharmacology[21,22] is one attempt to integrate these factors to help anticipate therapeutic roadblocks and pitfalls. It emphasizes how to prescribe rather than what to prescribe. It complements the traditional objective-descriptive approach of prescribing that considers how patients are similar (diagnostic criteria) and explicitly acknowledges, incorporates, and addresses the central role of meaning and interpersonal factors in psychopharmacology. Psychodynamic psychopharmacology is organized around six technical principles. Whereas these six principles are informed by a psychodynamic attitude, they are applicable in any treatment setting. These principles are the organizing framework for this article, although many or most of the recommendations here could not be considered the sole province of psychodynamics.

1. Avoid mind-body split.
2. Know who the patient is.
3. Attend to ambivalence about loss of symptoms.
4. Cultivate the therapeutic alliance.
5. Attend to countertherapeutic uses of medications.
6. Identify, contain, and use countertransference.

AVOID A MIND-BODY SPLIT

Think Integratively, Not Reductionistically

It seems likely that a first step, before making any behavioral interventions that might facilitate treatment, involves developing an attitude toward pharmacotherapy that integrates biological and psychosocial perspectives. Most fundamentally, a prescriber must grasp that depression and recovery represent interplays of biological and psychosocial factors that are so complex that a full understanding is likely to elude doctor and patient. For example, when a patient benefits following the introduction of a new antidepressant, it is impossible to know the relative contributions of the active medication, the placebo effect, the alliance, the patient's expectations and desire for change, and a multitude of other factors. However, an ability to

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respond flexibly to meaning factors in psychopharmacology and to use them to enhance outcomes is conditioned on an ability to hold an integrated perspective.

This response and use may be easier said than done, because there are many pressures toward reductionism in the practice of psychopharmacology. Culturally, mind-body dualism is embedded in Western metaphors since Descartes at least and constrains our possibilities of thought. On a personal level, doctors may be pulled toward a reductionistic understanding to escape anxiety and ambiguity or because a simplified field allows the doctor to address the patient with greater certainty and authority. Professional pressures to fall onto one side of the mind-body split include allegiances to a particular model of treatment (eg, biological vs psychotherapeutic) underlying metaphors in medicine[23] as well as pressures intrinsic to the current model of health care delivery (ie, managed care), which often pushes biologically focused or split treatments. How often, for example, in a managed care review, does the treater face pressure to add another medication when a more helpful intervention would be to assist the patient in addressing a family member about some intolerable aspect of his or her living situation? Reductionistic pressures may also derive from patients, particularly when they are defensively invested in the experience of not being responsible for illness behaviors[21] and, thus, present their symptoms in the form of an argument for a biological explanation.

Recognize the Patient as Both Subject and Object

Within the psychoanalytic paradigm, patients were seen as responsible for the production and alleviation of symptoms. This position, when held dogmatically, had the potential to leave the patient feeling blamed for the illness. Under the sway of a more biological model, patients are more likely now to be seen as victims of an inexorable biology and treated as if they have no internal resources that they can recruit in the service of recovery. The treatments that follow (the prescription of an antidepressant) invest all of the healing power in the doctor and his tools. Instructions regarding the proper use of medications are too infrequently buttressed with adequate instruction regarding healthy behaviors on the part of the patient.[24]

Much is lost when the patient is not seen as a potential agent and ally in the process of recovery. Ironically, it is often not in psychiatry but in primary care medicine and related fields that “bio” gets linked with “psychosocial” in the recognition that the way the patient lives and approaches the illness can make all the difference between a treatment success and a treatment failure. As with diabetes or hypertension, the treatment contract for patients with depression should emphasize that patients have a central role in managing the disease, maximizing patients’ authority in relation to their illness.

There are a variety of lifestyle factors that can impact the outcome of depression. These are often neglected in favor of purely pharmacologic approaches. In addition to psychotherapy, lifestyle variables such as exercise,[25] adequate social supports,[26] and religion[26] have all been shown to enhance outcomes with depression. By recognizing the patient’s agency, the prescriber and patient can multiply the tools in the treatment armamentarium and enhance the chances of a good outcome.

The prescriber might also recognize that the patient is not simply an ally in the treatment. Because of ambivalence about illness, secondary gains, or negative feelings about the doctor, treatment, or medication, the patient may also be an adversary.[21] Recognition of these aspects of the patient’s subjectivity may allow mental health professionals to address and ameliorate those resistances to treatment.

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Consider Nonpharmacologic Factors in Treatment Response

When a patient improves on medications, or fails to improve or worsens, it may be useful (and it is certainly the most honest) to recognize that the reasons are always somewhat obscure. The patient's improvement on an antidepressant may be related to the medication's direct effects on serotonin and other neurotransmitters. However, it is just as easily attributable to the placebo response,[3–5] the treatment alliance,[6,27–29] the patient's expectations and wishes, and a myriad of other nonpharmacologic factors. Similarly, if a patient worsens on medications, it may be the result of side effects but could just as easily represent a nocebo response (see following), a defensive reaction, or a manifestation of disempowerment based on meanings attributed to treatment. Keeping these possibilities in mind helps treaters resist the pull to biological reductionism and to remain flexible in their thinking and approach to patients.

Incorporate Psychosocial Factors in the Treatment Agreement

Providing informed consent and educating the patient about his or her illness can involve educating the patient about potency of psychosocial factors in psychopharmacology. Depending on the patient's needs, this education may include discussions of the power of the placebo effect, treatment alliance, the patient's expectancies, and desire for change. The ultimate task here is to balance the instillation of hope with an honest and realistic humility regarding the actual limitations of our medications. Patients are thus encouraged to mobilize their own agency and become partners in the pursuit of health.

Construct an Integrated Treatment Frame

With fewer psychiatrists providing psychotherapy, split treatments have become the norm. If the prescriber and therapist differ widely in their beliefs about medications and goals of treatment, it is not likely that their shared patient will recover, especially if this disagreement is communicated in any way to the patient. However, just because a treatment is split does not mean that it is unintegrated, fragmented, or conflictual. Collaborative working relationships involving shared goals, a supportive position toward other health care providers' work, and necessary communication are possible and important, particularly when working with patients with treatment-refractory depression or significant character pathology. A broad evidence base suggests that models of collaborative care, which might include teamwork between therapists and prescribers[21,22] or comprehensive treatment teams involving physician extenders,[30] which provide more opportunities for clinical contact, have been shown to significantly improve outcomes in depressed patients. It is also worth noting that combined treatments, with one provider administering both medications and psychotherapy, are not necessarily integrated. A single provider can easily wear these two hats in such a way that pharmacologic and psychotherapeutic approaches are almost completely divorced.

KNOW WHO THE PATIENT IS

Within a biologically reductionistic model, the prescriber is concerned primarily with what the patient is (ie, the clinical diagnosis). Knowledge of the clinical characteristics of the depression (duration, severity, recurrence, clinical features, and somatic sensitivities) can certainly help the prescriber know what to prescribe for the average patient but may not adequately guide the doctor in prescribing for this unique patient with his or her particular history, character, and concerns. There are a variety of

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Table 2
Patient characteristics affecting treatment outcome

Patient Characteristics	Evidence
Neuroticism	Joyce & Paykel,[31] 1989
	Scott et al,[32] 1995
	Bagby et al,[26] 2002
	Steunenberg et al,[33] 2010
Defensive Style	Kronström et al,[34] 2009
Locus of Control	Reynaert et al,[35] 1995
Autonomy	Peselow et al,[36] 1992
Sociotropy	Peselow et al,[36] 1992
Social Disadvantage	Hahn,[37] 1997
Acquiescence	McNair et al,[38] 1968
	McNair et al,[39] 1970
	Fast & Fisher,[40] 1971
Attachment Style	Ciechanowski et al,[41] 2001
	Ciechanowski et al,[42] 2006
	Comninos & Grenyer,[43] 2007
Expectations of Treatment	Meyer et al,[44] 2002
	Krell et al,[45] 2004
	Aikens et al,[46] 2005
	Gaudiano & Miller,[47] 2006
	Sneed et al,[48] 2008
Treatment Preferences	Lin et al,[49] 2005
	Iacoviello et al,[50] 2007
	Kocsis et al,[51] 2009
	Raue et al,[52] 2009
	Kwan et al,[53] 2010
Ambivalence About Medications	Sirey et al,[54] 2001
	Aikens et al,[55] 2008
	Warden et al,[56] 2009
Secondary Gains Associated With Illness	van Egmond & Kummeling,[57] 2002
Autonomous Motivation for Treatment	Zuroff et al,[58] 2007
Readiness to Change	Beitman et al,[59] 1994
	Lewis et al,[60] 2009

nonclinical patient characteristics (**Table 2**) that affect pharmacologic treatment outcome. Understanding the patient more fully can help the prescriber to know not only what to prescribe, but how to prescribe it.

Personality and Temperament Factors Affecting Pharmacologic Outcomes

A wide variety of psychological and psychosocial factors have been shown to impact outcome in the pharmacologic treatment of depression (see **Table 2**). Neuroticism, a characterologic tendency toward worry and dysphoria coupled with relatively immature defenses was among the first personality characteristics found to impact pharmacologic treatment outcome. The vast majority of studies examining the

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relationship between neuroticism and pharmacologic treatment outcome have found negative correlations in both short-term and long-term response to antidepressant treatment,[31,32] as well as risk of recurrence.[33] This result is consistent with other findings that immaturity of defenses is a poor prognostic sign for psychopharmacologic treatment.[34] Curiously, a few studies conducted since 2000 have not found a correlation between neuroticism and pharmacologic nonresponse.[61,62] It is not clear why these later studies show different results, although they may reflect the particular measurement instrument used in these contemporary studies.

Autonomy (a sense of self-efficacy) and sociotropy (an orientation toward others for assistance and focus on pleasing others so as to secure interpersonal attachments) are personality characteristics that have also been found to impact pharmacologic treatment outcome, the former directly and the later inversely.[36] Patients exhibiting high autonomy and low sociotropy showed a response rate of 74.1% to antidepressant, whereas high-sociotropic/low-autonomous patients responded at half that rate (38.5%). It is intriguing to consider that sociotropic patients may paradoxically impair themselves in the context of pharmacologic treatment, handing too much responsibility for cure over to the doctor and emptying themselves of personal efficacy. Similarly, patients with an internal locus of control also fare significantly better with antidepressants than patients with an external locus of control.[35]

Attachment styles,[63] defined as fundamental modes of relating to others that are shaped in part by early caregiving relationships, also significantly affect the ways that medications are used. People with secure attachments are able comfortably to connect to and separate from important others and have a basic sense of trust. Anxious-fearful attachment patterns, similar to sociotropy, are characterized by an anxious attachment and worries about evoking a negative response from important others. People with dismissive or avoidant attachments, on the other hand, readily disconnect from others at the first disappointment. These are the "one strike and you're out" patients who often show particular difficulty with treatment adherence,[41] Patients with disorganized attachments are comfortable neither in proximity nor at a distance and tend to experience chaotic shifts in relationships as a result. Patients with secure attachments show an earlier response to antidepressants[43] compared with patients with fearful attachments.

An understanding of the patient's attachment style may guide treatment decisions. Difficulties with adherence that are associated with dismissive attachments can be reversed by particularly good communication on the part of the doctor.[41] These patients may also respond better to a team-based collaborative care approach[42] that offers extended support.

Patient Expectations of Treatment

Patients who expect more from pharmacologic treatment are likely to reap more benefits from it. This expectation is the reason that placebo controls are necessary in pharmacologic research. Patients who are enrolled in studies in which they know they will receive an antidepressant show antidepressant response rates of approximately 60%. The antidepressant response rate drops to 46% when patients are aware that they might receive placebo.[48]

The unique expectations that a patient brings to treatment also exert a significant effect on outcomes. For example, Krell and colleagues[45] found that patients with high expectations of pharmacologic treatment showed an impressive 90% antidepressant response rate, whereas patients who had only moderate expectations of treatment responded only 33% of the time. This effect was not moderated by adherence. Aikens and colleagues[46] found that initial skepticism about the appropriateness of pharmacologic treatment resulted in

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significant increases in antidepressant discontinuation (although, curiously, these skeptical, nonadherent patients did not have worse outcomes). The vast majority of other studies examining the role of expectations, however, have found a correlation between high expectations and outcome, although this effect may be moderated through effects on the therapeutic alliance in the treatment of major depression[44] or bipolar disorder.[47]

There are several technical implications of these findings. One is that it can be helpful to discuss a patient's expectations of treatment, which can inform patient and doctor about prognosis and provide opportunities to address irrational expectations that interfere with treatment response. The doctor can also use psychoeducational and supportive strategies to increase expectations. Such an intervention is incorporated into the model of interpersonal psychotherapy,[64] in which treaters are directed to encourage patients regarding their prognosis. When skepticism about medications is deeper and more irrational, psychotherapeutic interventions may be needed to enhance expectancies (eg, helping a patient differentiate himself or herself from a chronically mentally ill parent who failed to benefit from medications).

Nocebo Responders

Just as patients who expect to be helped benefit especially from medications (the placebo response), patients who harbor explicit or unconscious expectations of harm are more likely to develop side effects from medications (the nocebo response). Whereas it is not a simple matter to differentiate chemical sensitivity and abnormalities in drug metabolism from nocebo responsiveness, there are a number of psychosocial factors that are known to predispose patients to side effects. Most directly, there are conscious expectations of harm. Such expectations could be elicited in discussions of patient expectations of treatment. More neurotic patients may be prone to increased side effect reporting.[65] An experience of powerlessness seems also to be particularly fertile ground for nocebo responses. Individuals from socially disadvantaged groups (minorities, women, low socioeconomic status) are more nocebo-prone,[37] as are acquiescent patients.[38–40] Acquiescence is a personality trait of easily surrendering to the will of others. It is as if these patients, unable to say no with their voices, do so instead with their bodies. Discussing the conditions of nocebogenesis before side effects emerge may give the patient and doctor some room to think about options (besides discontinuation) if side effects emerge.[8,21]

CULTIVATE THE PHARMACOTHERAPEUTIC ALLIANCE

Although every medical student learns that the doctor-patient relationship (**Table 3**) is of central importance in the practice of medicine, it typically receives far less attention than the more specific treatments that the doctor offers. However, given that the therapeutic alliance seems to contribute more potently to pharmacologic treatment outcomes than does the actual drug used,[6] it is essential to focus on and cultivate a strong therapeutic alliance. This effort toward alliance means not only gaining the patient's respect through a combination of competence, presence, tact, and empathy, but also respecting the patient's capacities as a participant in the therapeutic endeavor and actively engaging conditioned distortions (transferences) that the patient brings into pharmacotherapy regarding prescribers and/or caregiving figures in general.

Support the Patient's Agency

One potential danger of pharmacologic treatment of depression is that the patient, feeling stricken by a biological disease beyond his or her control, may surrender

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Table 3
Characteristic of the doctor-patient relationship promoting improved outcomes

Outcome-Enhancing Characteristics of the Doctor-Patient Relationship in Pharmacotherapy	Evidence
Overall Effectiveness of the Doctor	McKay et al,[7] 2006
The Doctor's Positive Attitude About the Medication	Downing et al,[20] 1973
Therapeutic Alliance	Krupnick et al,[6] 1996
	Weiss et al,[27] 1997
	Klein et al,[28] 2003
	Blatt & Zuroff,[29] 2005
Good Communication	Lin et al,[66] 1995
	Bultman & Svarstad,[24] 2000
	Bull et al,[67] 2002
Involvement of the Patient in Decision-Making	Clever et al,[68] 2006
	Loh et al,[69] 2007
	Woolley et al,[70] 2010
Agreement About Diagnosis	Woolley et al,[70] 2010
Autonomy-Promoting	Zuroff et al,[58] 2007

personal agency, passively awaiting cure by the doctor's medications. Such a passive orientation does not bode well for the patient. Patients who are sociotropic[36] or who manifest an external locus of control[35] are less likely to benefit from antidepressant treatment. Conversely, patients who view their depression as nonbiological seem to benefit more from antidepressant treatment, at least for milder forms of depression.[71]

Biologically reductionistic explanations of the patient's illness, although relieving more masochistic patients of self-blame, may in the long run promote treatment resistance. The negotiation of a treatment agreement is a complicated process, instilling hope while maintaining a realistic humility about the limits of medications, and emphasizing the role that patients can play in their own recovery while sensitively trying to help them not to feel blamed for illness.

The attitude and behavior of the prescriber can have wide-ranging effects on patients' relationship toward their illness and treatment. Patients who perceive their doctors as supporting their autonomy feel more inwardly (as opposed to externally) motivated for treatment. This in turn is a strong predictor of treatment outcome; perhaps even stronger than therapeutic alliance itself.[58]

Alliance, Not Compliance

In pharmacotherapy, it is not uncommon for alliance to be confused with compliance[72] and for patients to be seen as in alliance with the doctor when they take their medication. Conversely, patients may also believe they have a good alliance with their doctor when the doctor gives them the medications they want, regardless of the physician's misgivings. Alliance, however, is a two-way street, a negotiation in which neither participant submits to the will of the other and both find a way to feel invested in the treatment plan. The model of doctor as ultimate authority on the patient's health is frequently more harmful than helpful. Similarly, is it not useful to conceptualize the doctor as servant, because the customer is not always right. A model of shared inquiry and partnership is ideal and seems to promote long-term adherence.[73]

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Focus on Communication

Communication style and skills are important ingredients of a therapeutic alliance. Effective doctor-patient communication is not only clear but also collaborative, involving active listening and a nonauthoritarian orientation to problem-solving and conflict resolution.[24] Clear and collaborative communication enhances medication adherence.[24,66] Skilled communication may be especially important with specific populations, such as patients with a dismissive attachment style.[41] Discussions regarding medication should have clear explanations regarding time course of response and recommended duration of treatment.[66] Discussion of anticipated side effects also promotes adherence.[67] Many of these recommendations border on the obvious but can easily be neglected by the harried provider. Less obvious, perhaps, is the finding that adherence is increased when communication with the depressed patient involves encouragement to engage in pleasurable activities.[24,66]

Elicit Patient Preferences for Type of Treatment

Within the bounds of reason and conscience, it is useful to give the patient the treatment that he or she wants, particularly if the patient holds strong preferences for one form of treatment over another.[52] When patients prefer medications to psychotherapy, they should be offered medications. The converse is even more true: patients who prefer psychotherapy should be offered psychotherapy, because they are unlikely to benefit from medications. Kocsis and colleagues[51] found that patients receiving their preferred treatments remitted approximately 45% to 50% of the time. However, when receiving nonpreferred treatments, patients getting psychotherapy showed a 22.2% remission rate, whereas patients receiving medications remitted only 7.7% of the time. Patients receiving preferred treatments seem also to benefit more rapidly than patients receiving nonpreferred treatments.[49]

It may be that treatment preferences exert their effects on outcome indirectly through effects on other variables such as adherence and alliance. Patients assigned to nonpreferred treatments are more likely not even to start treatment and are more likely to drop out after starting,[52] particularly when treatment preferences are strong. Additionally, patients receiving nonpreferred treatments attend fewer scheduled appointments with treaters, accounting for as much as 16% of outcome variance,[53] whereas those receiving medications who prefer psychotherapy show significant decreases in alliance over the course of treatment.[50]

Involve the Patient in Decision-Making

Beyond the type of treatment (medications vs therapy), there are other ways to involve the patient in decision-making, including selection of treatment goals, medication, and dosing schedule. Involving the patient in this way enhances the alliance and increases patient satisfaction with treatment.[69]

More important, involving the patient in treatment decisions enhances utilization of treatment. In one study,[70] depressed inpatients and outpatients who were involved in treatment decisions were 2.3 times more likely to continue taking their medications. These patients were also twice as likely to discontinue treatment when they did not agree with the doctor's diagnosis. When patients disagreed with the diagnosis and felt uninvolved in decision-making, they were 7.3 times more likely to discontinue treatment against recommendations. Patients involved in decision-making have substantially better 18-month treatment outcomes,[68] with the degree of involvement directly correlated with the degree of improvement. Involving patients in decision-making also

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benefits treatments in more subtle ways, promoting treatment regimens that are ultimately more guideline-concordant.[68]

Even involvement in relatively minor treatment decisions such as the dosing schedule for the medication can exert significant effects. For example, patients given a choice between once daily and 3 times daily dosing of an antidepressant medication were significantly more likely to adhere to prescribed regimens. It is perhaps worth noting that such a negotiation is a place where the doctor might make rational concessions to the patient's irrational wishes for the sake of promoting an alliance and a positive outcome. The art of forging an alliance often involves thoughtfully choosing one's battles.

The busy prescriber might protest that there is insufficient time to elicit patients' preferences and involve them in clinical decision-making. However, the available evidence suggests that this negotiation does not actually increase the time required for a consultation.[69]

Increase the Dose . . . of the Doctor

When patients fail to respond to medications, common treatment algorithms might suggest an increase in medication dose to a therapeutic maximum, if not beyond. However, it might be just as helpful to make alliance-enhancing interventions such as increasing the dose, not of the medication, but of the doctor.[74] More frequent contact with treaters is likely an ingredient of a strong alliance and a factor in improved antidepressant adherence.[67] This benefit may be especially true when frequent contact is paired with a supportive environment and involvement with family members.[73] Indeed, it may be that nonpharmacologic factors, such as regular contact, are of sufficient importance that a treatment cannot truly be called evidence-based unless it follows the meeting schedule of the original study that forms the evidence base,[74] a schedule that typically involves weekly or biweekly meetings with the doctor or the doctor's representatives.

Address Problems in the Alliance/Negative Transferences

Either as a result of previous experiences with medications and caregivers or unconstructive interactions with the current prescriber, patients may harbor negative feelings toward the doctor. These feelings are often not articulated and may not even be conscious. These negative feelings may be expressed as poor adherence, treatment nonresponse, or nocebo effects. The maintenance of an alliance requires the prescriber to develop comfort with hearing the patient's criticism and negative feelings and the ability to address those feelings nondefensively. It may be helpful to remember that in any enduring relationship, injuries, however small, will always occur.

ATTEND TO THE PATIENT'S AMBIVALENCE

Patients may be ambivalent about their doctors. This ambivalence may emerge from transference-based expectations of caregivers or may be the result of problems in the real relationship between doctor and patient, or both, and may lead patients to resist treatment. It is more common that patients are ambivalent about their medications. This ambivalence may be particularly ubiquitous regarding psychiatric medications, which carry the standard side effect risk common to all medications but are also infused with threats to identity and stigmatizing social meanings.[75] Not surprising, perceived stigma is known to predict antidepressant nonadherence.[54]

In a content analysis of patients' representations of antidepressant medications, ambivalence was the most common of 15 themes to emerge.[76] In the average patient,

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perception of dangerousness and addictiveness easily balanced therapeutic effects. Whereas 44% saw antidepressants as soothing and 39% saw them as improving mood, 47% saw them as causing dependence, and 56% saw them as having adverse effects. Often the deck is stacked against medication adherence before the patient even begins treatment. Patients who express early ambivalence are twice as likely to discontinue medications prematurely and three times more likely to stop medications prematurely in the context of side effects.[56]

Inquire Specifically About Ambivalence

Given potential risks of medications (both somatic and psychosocial), the prescriber knows that patients have reason to be ambivalent. However, to understand the varying degrees of ambivalence and patterns of ambivalence, it is important to ask. The types of questions are important, because they yield very different types of information. When patients are asked broad, general questions about ambivalence toward medications, only 2% to 4% will identify ambivalence about taking medications as a significant issue. However, when asked more specific questions (eg, if you develop side effects, how likely are you to stop medications, or if you perceive no benefits in 1 month, how likely are you to stop), 23% to 36% of patients will signal their ambivalence.[56]

Inoculate the Ambivalent Patient

Like the patient with a dismissive attachment style,[65] these ambivalent patients may require particular attention and very clear communication. Patients who worry about side effects may benefit from knowing that the prescriber is sensitive to and concerned about side effects, and adherence may be increased with thorough psychoeducation about the time course of side effects (especially when tolerance is likely to develop to side effects) and strategies to manage side effects. Similarly, the ambivalent patient especially needs to understand that lack of immediate benefit does not signal a negative outcome and that these medications typically take 3 to 6 weeks to show a beneficial effect.[56] Some prescribers may seek to avoid discussions of potential side effects in an effort not to generate further ambivalence. It seems, however, that it is better to address these issues head-on. When adverse reactions are discussed with the prescriber, patients are actually less likely to discontinue antidepressants.[67]

Shape Prescribing Strategies to the Patient's Ambivalence

In a thoughtful and well-controlled study of ambivalence, Aikens and colleagues[55] explored medication adherence as a function of the patients' reasoned assessment of the balance of risks and benefits. The investigators identified four categories of patients. Depressed, medication-accepting patients saw antidepressants as necessary and were not particularly concerned about negative effects. At the opposite pole, skeptical patients had low expectations of antidepressants and high degrees of concern. Ambivalent patients saw medications as necessary for treatment of depression but also were quite concerned about the potential for negative consequences. The fourth group, indifferent patients, were not especially worried about medications, but neither did they expect much. The investigators suggest that each of these types of patients would benefit from a different treatment strategy. Accepting patients are likely to adhere to medications, whatever the approach. Indifferent patients will need to see results to be convinced of the importance of adherence. Because they are not especially concerned about side effects, an aggressive built-for-speed approach

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designed to bring about a rapid and complete response may be preferable. On the other hand, ambivalent patients, whose adherence is affected by concern about side effects, may benefit more from a start low, go slow approach that is designed-for-comfort. Skeptical patients may best be treated with nonpharmacologic interventions unless their illness unfolds in such a way as to increase their perceived need for medications or psychotherapeutic interventions ameliorate negative transferences or dysfunctional attitudes about medications.

Ambivalence About Illness

Perhaps more insidious and difficult to treat are those cases in which the patient is ambivalent not so much about medications as about getting better. A traditional conceptualization of medical illness takes for granted that the patient wants to get better. Whereas it is true that patients vote with their feet when they seek treatment, it is worth challenging this basic assumption.

Studies of illness benefits (or secondary gain) suggest that approximately half of patients can identify secondary benefits that derive from the sick role and/or treatment-seeking.[77,78] A study involving depressed students and psychiatric outpatients found that 44% of students and 64% of community participants identified benefits to their illness.[77] The health implications of this result are significant, because patients who expect some gain from their illness are much less likely to experience remission of symptoms.[57] When patients are treatment-refractory, ambivalence about illness should be considered as a possible source of treatment resistance.

Maintain Neutrality and Empathy

Whereas sometimes there is an overt and cynical interest in remaining (or acting) ill (eg, in order to secure remuneration for illness), secondary gains from the sick role are often subtle and may not even be conscious. Patients who become truly depressed typically do not do so in order to derive secondary gains; however, once ill, they may discover that the sick role confers certain benefits. The dynamic model of symptoms as partial solutions becomes useful in this regard. Symptoms and illness behaviors may come to represent the patient's best effort at managing overwhelming affect, communicating something that cannot be put into words or allowing for the assumption of a role in a family that would otherwise be intolerable.[21]

These patients often evoke frustration, if not condemnation, from treaters, and the capacity of treaters to remain empathic is often strained. It is perhaps useful to remember that patients who cleave to the sick role generally do so at tremendous personal cost to themselves. To understand the reasons that patients would give up so much for the seemingly meager benefits of the sick role is to restore empathy and establish a therapeutic frame in which a true exploration of ambivalence can occur.

The patient's ambivalence about recovery is not presented readily. Although 42% of patients seeking psychiatric help expect some secondary gain from treatment, only 9% reveal this expectation to their treaters.[78] It can be useful to inquire, during the initial assessment phase of pharmacotherapy, about what a patient stands to lose if treatment works. It is less useful to ask the same question later in treatment, because it is then more likely to come from a place of frustration, sparking the patient's defensiveness and shutting down awareness of ambivalence.

Even with the treater's sensitive curiosity, patients may not be willing to say (or know) they are ambivalent. Patients often feel ashamed or humiliated by a conscious wish to remain sick. More often, however, these aspects remain largely out of the patient's awareness. Generally, psychotherapeutic interventions are called for if patients are to get to a place where they might best be able to make use of

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medications in the service of recovery. An appreciation by the treater for the patient's ambivalence about the loss of symptoms may also influence the timing of interventions (pharmacologic or psychotherapeutic), because there is some evidence that a patient's readiness to change may be a powerful variable in treatment response.[59,60]

It is through attentive, nonjudgmental, and open investigation that the patient may begin to connect with underlying ambivalence. These investigations, aimed at a fuller appreciation for the patient's current situation and underlying motivations, are an essential aspect of working collaboratively with a patient. In the course of these explorations, patients may be helped to see more clearly their attachment to the sick role and the losses they have experienced as a result of that attachment. In addition to social costs, there may be psychological costs (such as guilt over unearned benefits of the sick role) that enter into the patient's changing understanding of the economy of gain.[79] These explorations can enhance alliance, which can improve pharmacologic outcome on its own.[6] The adoption of a neutral, curious, and empathic stance can be difficult to achieve and may be nearly impossible when patients or social systems put the treater in the position of gatekeeper for access to concrete rewards for illness (eg, disability benefits).

ADDRESS COUNTERTHERAPEUTIC USES OF MEDICATIONS

Clinicians are often attentive to signs that their patient is misusing a prescribed medication that has effects on the brain's reward systems (opiates and benzodiazepines in particular). Physicians are less likely to consider medication misuse when those medications are not seen as rewarding or intoxicating, such as occurs when patients use antipsychotics recreationally.[80] It may be harder still to identify signs that a prescribed medication has been turned to serve more subtle countertherapeutic ends, particularly when the patient experiences the medication as helpful and there is evidence of attenuation of some symptoms.

Treatment Resistance from Medications

One sign of a countertherapeutic use of medications might be when a patient who feels better with certain medications does not seem to get better. Overall functioning does not improve, or worsens, or perhaps the prescriber merely senses, with a feeling of apprehension or guilt, that the patient is in the process of becoming chronic. In these cases it is useful to consider whether medications are being used in ways that interfere with the developmental task of treatment.

There are a number of ways that prescribed medications may unintentionally contribute to treatment resistance. In some cases the medication (or the diagnosis that comes with the medication) may serve as an inexact interpretation[81,82] that patients seize on to bolster unhealthy defenses, interfering with the patient's adaptability or self-awareness.

One common example of this inexact interpretation is when primitively organized and character-disordered patients who rely on splitting and projective dynamics receive a prescription of mood stabilizers for bipolar disorder. Such patients tend to see things strictly in black and white and often defend against feeling intolerably and completely bad by displacing all of the "badness" onto the "other" in a relationship. Such a patient, prone to splitting as a defense, will often experience an immediate reduction in dysphoria at receiving a bipolar diagnosis. A psychopharmacologist who is inclined to think both psychodynamically and biologically will recognize that the reduction in dysphoria may be occurring not because of the medication but because it allows the patient to create a stable split within which he or she can remain good, while all badness is located in "my bipolar." Although patients may feel better, they

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actually do worse. No longer feeling personally responsible for symptomatic behavior, they give their worst instincts free rein, exacerbating personal and interpersonal chaos. Substances can be used defensively to disavow responsibility for feelings and actions.[83]

Medications can be used defensively in myriad other ways. Patients who experience people as dangerous and unreliable may attempt to replace people with pills, turning to medications instead of people to deal with ordinary frustrations and injuries. Although pills may help them to manage, their medicalized universe becomes increasingly depopulated. This patient is not likely to emerge from depression. Still other patients may believe that any negative feeling is pathologic and should be extinguished. In a sense, these patients no longer have feelings that they should learn from. Instead they have symptoms that become the purview of the doctor. If accepted at face value, this situation can lead a well-meaning psychiatrist toward an ever more complex and burdensome medication regimen that actually contravenes healthy developmental aims.

When pills are used to manage developmentally appropriate feelings like loneliness, disappointment, sadness, frustration, or anger, patients lose important opportunities that might lead to improved internal controls and increased affective or interpersonal competence. Patients who turn too much to their doctors to solve their problems of living may not only be treatment-resistant *to* their medications but also may become treatment resistant *from* their medications.[35,36,71]

Think Like a Mental Health Professional

One's ability to recognize countertherapeutic uses of medications may be conditioned on one's conceptualization of the therapeutic task. With a singular focus on symptoms and symptom reduction, a great many providers have inadvertently become mental *illness* professionals, pursuing symptoms while losing sight of larger developmental aims. In contrast, a mental *health* professional is concerned not just with the absence of illness, but even more with the promotion of health. By prescribing in a way that fosters the patient's agency and overall adaptive capacity, a mental health professional does not miss the forest for the trees and is more likely to be attuned to defensive and disempowering uses of medications.

IDENTIFY AND CONTAIN COUNTERTRANSFERENCE PRESCRIBING

A hallmark of countertransference prescribing is its focus on managing the experience of the prescriber rather than the experience of the patient. Although the image of a rational and methodical prescriber may be appealing, the emotional response of the prescriber is sometimes the primary impetus for a prescription.[84] Especially in those cases in which the patient's dysphoria is infectious, provoking intense feelings of anger, hopelessness, helplessness, or even despair in the doctor, prescriptions may unconsciously be aimed at decreasing those feelings. In the same way that resistance from medications interferes with the developmental task of treatment, unexamined countertransference prescribing runs the risk of becoming a chronic form of nontreatment. Understood, however, instances of countertransference prescribing can become valuable sources of data about the patient's experience and relationships outside the treatment.

Colleagues are Crucial

Managing the impulse to prescribe out of countertransference or recognizing that one is already prescribing out of countertransference often requires an outside perspective. The role of consultation with other colleagues cannot be underestimated when

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working with patients who evoke strong countertransference reactions. Systems, however, are in no way immune to prescribing enactments in the face of strong feelings.[85] Colleagues with some distance from the intensity of the case can best offer a connection to a standard of practice that a prescriber can lose touch with amid an enactment.

Develop a Dynamic Formulation

A dynamic formulation can also exert a containing and conservative effect, orienting the prescriber and others under the pressure of strong disorganizing affect. A self-aware prescriber with a formulation of repetitive patterns in the patient's life will be more likely to anticipate prescribing enactments (eg, when the prescriber recreates the dynamic of the parents who cannot tolerate the strong affects of their child). A dynamic formulation may also help providers to maintain empathy toward the patient. Both psychodynamic and cognitive-behavioral formulations of symptoms have empathogenic effects. However, benefits accruing from a psychodynamic formulation seem to persist, whereas the benefits of cognitive-behavioral understandings decline to nonsignificance over time.[86]

A dynamic formulation need not be a thousand-word document. A brief focused formulation of the patient's relationship to medications and/or treaters is generally sufficient for the prescriber. Such a formulation might, for example, predict that a patient with deep-seated issues around control would attempt to wrest control of the medications from the doctor or anticipate that a patient who could neither bear nor articulate a desperate feeling of helplessness would powerfully evoke that same feeling in the treater. When in the thrall of strong countertransference feelings the prescriber can then call on the formulation, which may allow the prescriber to identify and contain potential irrational processes in the pharmacotherapeutic relationship.

Similarly, a dynamic formulation that contains a systems perspective, if shared, can help the prescriber to contain irrational processes in the larger treatment system. If this sharing works well, the prescriber will benefit from only having to deal with uncontained irrationality on one front: the patient. A brief dynamic formulation, included in the patient's chart, is also a way to pass on accumulated wisdom about a patient and to inoculate future treaters from predictable enactments.

SUMMARY

Despite advances in psychopharmacology over the past several decades, treatment outcomes for depression have not substantially improved. Depression is not being eradicated. If anything, the evidence suggests that the problem of depression and treatment-resistant depression is growing, not shrinking.[87] As biologically reductionistic approaches dominate psychiatric practice, patient care has steered away from considering the potent effects of meaning and relationships in the psychopharmacologic treatment of our patients. By construing patients as passive recipients of concrete, specific, and straightforward medical interventions, the field has succumbed to a delusion of precision,[88] and unwittingly moved into an era of treatment resistance in which some of our most potent tools are wasted. In such a model we have settled for treating a disorder rather than a whole person. This article is intended as a step toward remedy. Meaning effects, therapeutic alliance, ambivalence, and patient autonomy, among others, have a powerful and measurable impact on the use of medication that should be considered if we are to treat the whole person. Bringing these elements together into a coherent model of treatment, however, is only a starting point. More research is needed if we are to understand the effects these elements have when used together in an integrated model that is simultaneously personalized and evidence-based.

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REFERENCES

1. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163:28–40.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006;354:1231–42.
3. Kirsch I, Sapirstein G. Listening to Prozac but hearing placebo: a meta–analysis of antidepressant medication. Prevention and Treatment 1998;1(2):Article 2a.
4. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. Arch Gen Psychiatry 2000;57:311–7.
5. Kirsch I, Moore TJ, Scoboria A, et al. The emperor's new drugs: an analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prevention and Treatment. 2002;5:Article 23.
6. Krupnick JL, Sotsky SM, Simmens S, et al. The role of therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol 1996;64:532–9.
7. McKay KM, Imel ZE, Wampold BE. Psychiatrist effects in the psychopharmacological treatment of depression. J Affect Disord 2006; 92:287–90.
8. Mintz D. Meaning and medication in the care of treatment-resistant patients. Am J Psychother 2002;56:322–37.
9. Plakun EM. A view from Riggs: Treatment resistance and patient authority: I. A psychodynamic perspective. J Am Acad Psychoanal Dyn Psychiatry 2006;34: 349–66.
10. Mojtabai R, Olfson M. National trends in psychotherapy by office-based psychiatrists. Arch Gen Psychiatry 2008;65,962–97.
11. Chong WW, Aslani P, Chen TF. Effectiveness of interventions to improve antidepressant medication adherence: a systematic review. Int J Clin Pract 2011;65:954–75.
12. Rush AJ, Trivedi MH. Treating depression to remission. Psychiatr Ann 1995;25: 704–9.
13. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. Eur Neuropsychopharmacol 2007;17:696–707.
14. Thase ME, Friedman ES, Biggs MM, et al, Cognitive therapy versus medication in augmentation and switch strategies as second step treatments: a STAR*D report. Am J Psychiatry 2007;164:739–52.
15. Fisher S, Greenberg RP. The curse of the placebo: fanciful pursuit of a pure biological therapy. In: Greenberg RP, Fisher S, editors. From placebo to panacea. New York: Wiley; 1997. p. 3–56.
16. Schapira K, McClelland HA, Griffiths NR, et al. Study on the effects of tablet colour in the treatment of anxiety states. BMJ 1970;1:446–9.
17. de Craen AJ, Roos PJ, Leonard de Vries A, et al. Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. BMJ 1996;313:1624–6.
18. Waber RL, Shiv B, Carmon Z. Commercial features of placebo and therapeutic efficacy. JAMA 2008;299:1016–7.
19. de Craen AJ, Tijssen JG, de Gans J, et al. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. J Neurol 2000;247: 183–8.

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20. Downing RW, Rickels K, Dreesmann H. Orthogonal factors vs. interdependent variables as predictors of drug treatment response in anxious outpatients. Psychopharmacologia 1973;32:93–111.
21. Mintz DL, Belnap BA. A view from Riggs: treatment resistance and patient authority - III. What is psychodynamic psychopharmacology? An approach to pharmacologic treatment resistance. J Am Acad Psychoanal Dyn Psychiatry. 2006;34:581–601.
22. Mintz DL, Belnap BA. What is psychodynamic psychopharmacology? An approach to pharmacological treatment resistance. In: Plakun EM, editor. Treatment resistance and patient authority: an Austen Riggs reader. New York: Norton; 2011. p. 42–65.
23. Mintz, D. The distancing function of language in medicine. J Med Humanit 1991;13: 223–33.
24. Bultman DC, Svarstad BL. Effects of physician communication style on client medication beliefs and adherence with antidepressant treatment. Patient Educ Couns 2000;40:173–85.
25. Ströhle A. Physical activity, exercise, depression and anxiety disorders. J Neural Transm 2009;116:777–84.
26. Bagby RM, Ryder AG, Cristi C. Psychosocial and clinical predictors of response to pharmacotherapy for depression. J Psychiatry Neurosci 2002;27:250–25.
27. Weiss M, Gaston L, Propst A, et al. The role of the alliance in the pharmacologic treatment of depression. J Clin Psychiatry 1997;58:196–204.
28. Klein DN, Schwartz JE, Santiago NJ, et al. Therapeutic alliance in depression treatment: controlling for prior change and patient characteristics. J Consult Clin Psychol 2003;71:997–1006.
29. Blatt SJ, Zuroff DC. Empirical evaluation of the assumptions in identifying evidence based treatments in mental health. Clin Psychol Rev 2005;25:459–86.
30. Vergouwen AC, Bakker A, Katon WJ, et al. Improving adherence to antidepressants: a systematic review of interventions. J Clin Psychiatry 2003;64:1415–20.
31. Joyce PR, Paykel ES. Predictors of drug response in depression. Arch Gen Psychiatry 1989;46:89–99.
32. Scott J, Williams JM, Brittlebank A, et al. The relationship between premorbid neuroticism, cognitive dysfunction and persistence of depression: a 1-year follow-up. J Affect Disord 1995;33:167–72.
33. Steunenberg B, Beekman AT, Deeg DJ, et al. Personality predicts recurrence of late-life depression. J Affect Disord 2010;123:164–72.
34. Kronström K, Salminen JK, Hietala J, et al. Does defense style or psychological mindedness predict treatment response in major depression? Depress Anxiety 2009; 26:689–95.
35. Reynaert C, Janne P, Vause M, et al. Clinical trials of antidepressants: the hidden face: where locus of control appears to play a key role in depression outcome. Psychopharmacology 1995;119:449–54.
36. Peselow ED, Robins CJ, Sanfilipo MP, et al. Sociotropy and autonomy: relationship to antidepressant drug treatment response and endogenous-nonendogenous dichotomy. J Abnorm Psychol 1992;101:479–86.
37. Hahn RA. The nocebo phenomenon: concept, evidence, and implications for public health. Prev Med 1997;26:607–11.
38. McNair DM, Kahn RJ, Droppelman RF, et al. Compatibility, acquiescence, and drug effects. In: Brill H, editor. Neuro-psycho-pharmacology: proceedings of the Fifth International Congress of the Collegioum Internationale Neuro-psycho pharmacologicum. New York: Excerpta Medica Foundation; 1968. p. 536–42.
39. McNair DM, Fisher S, Kahn RJ, et al. Drug-personality interaction in intensive outpatient treatment. Arch Gen Psychiatry 1970;22:128–35.

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40. Fast GJ, Fisher S. The role of body attitudes and acquiescence in epinephrine and placebo effects. Psychosom Med 1971;33:63–84.
41. Ciechanowski PS, Katon WJ, Russo JE, et al. The patient-provider relationship: attachment theory and adherence to treatment in diabetes. Am J Psychiatry 2001; 158:29–35.
42. Ciechanowski PS, Russo JE, Katon WJ, et al. The association of patient relationship style and outcomes in collaborative care treatment for depression in patients with diabetes. Med Care 2006;44:283–29.
43. Comninos A, Grenyer BF. The influence of interpersonal factors on the speed of recovery from major depression. Psychother Res 2007;17:230–9.
44. Meyer B, Pilkonis PA Krupnick JL, et al. Treatment expectancies, patient alliance, and outcome: further analyses from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol 2002;70: 1051–5.
45. Krell HV, Leuchter AF, Morgan M, et al. Subject expectations of treatment effectiveness and outcome of treatment with an experimental antidepressant. J Clin Psychiatry 2004;65:1174–9.
46. Aikens JE, Kroenke K, Swindle RW, et al. Nine-month predictors and outcomes of SSRI antidepressant continuation in primary care. Gen Hosp Psychiatry 2005;27: 229–36.
47. Gaudiano BA, Miller IW. Patients' expectancies, the alliance in pharmacotherapy, and treatment outcomes in bipolar disorder. J Consult Clin Psychol 2006;74:671–6.
48. Sneed JR, Rutherford BR, Rindskopf D, et al. Design makes a difference: a meta-analysis of antidepressant response rates in placebo-controlled versus comparator trials in late-life depression. Am J Geriatr 2008;16:65–73.
49. Lin P, Campbell DG, Chaney EF, et al. The influence of patient preference on depression treatment in primary care. Ann Behav Med 2005;30:164–73.
50. Iacoviello BM, McCarthy KS, Barrett MS, et al. Treatment preferences affect the therapeutic alliance: implications for randomized controlled trials. J Consult Clin Psychol 2007;75:194–8.
51. Kocsis JH, Leon AC, Markowitz JC, et al. Patient preference as a moderator of outcome for chronic forms of major depressive disorder treated with nefazodone, cognitive behavioral analysis system of psychotherapy, or their combination. J Clin Psychiatry 2009;70:354–61.
52. Raue PJ, Schulberg HC, Heo M, et al. Patients' depression treatment preferences and initiation, adherence, and outcome: a randomized primary care study. Psychiatr Serv 2009;60:337–43.
53. Kwan BM, Dimidjian S, Rizvi SL. Treatment preference, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. Behav Res Ther 2010;48(8):799–80.
54. Sirey JA, Bruce ML, Alexopoulos GS, et al. Stigma as a barrier to recovery: perceived stigma and patient-rated severity of illness as predictors of antidepressant drug adherence. Psychiatr Serv 2001;52:1615–20.
55. Aikens JE, Nease DE, Klinkman MS, Explaining patients' beliefs about the necessity and harmfulness of antidepressants. Ann Fam Med 2008;6:23–9.
56. Warden D, Trivedi MH, Wisniewski SR, et al. Identifying risk for attrition during treatment for depression. Psychother Psychosom 2009;78:372–9.
57. van Egmond J, Kummeling I. A blind spot for secondary gain affecting therapy outcomes. Eur Psychiat 2002;17:46–54.

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58. Zuroff DC, Koestner R, Moskowitz DS, et al. Autonomous motivation for therapy: a new common factor in brief treatments for depression. Psychother Res 2007;17(2): 137–47.
59. Beitman BD, Beck NC, Deuser WE, et al. Patient stage of change predicts outcome in a panic disorder medication trial. Anxiety 1994;1:64–9.
60. Lewis CC, Simons AD, Silva SG, et al. The role of readiness to change in response to treatment of adolescent depression. J Consult Clin Psychol 2009;77:422–42.
61. Petersen T, Papakostas GI, Bottonari K, et al. NEO-FFI factor scores as predictors of clinical response to fluoxetine in depressed outpatients. Psychiatry Res 2002; 109:9–16.
62. Bos EH, Bouhuys AL, Geerts E, et al. Cognitive, physiological, and personality correlates of recurrence of depression. J Affect Disord 2005;87:221–2.
63. Bartholomew K, Horowitz LM. Attachment styles among young adults: A test of a four-category model. J Personal Soc Psychol 1991;61:226–44.
64. Klerman GL, Weissman MM, Rounsaville BJ, et al. Interpersonal psychotherapy of depression. New York: Basic Books; 1984.
65. Davis C, Ralevski E, Kennedy S, et al. The role of personality factors in the reporting of side effect complaints to moclobemide and placebo: a study of healthy male and female volunteers. J Clin Psychopharmacol 1995;15:5:347–52.
66. Lin EH, Von Korff M, Katon, W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 1995;33:67–74.
67. Bull SA, Hu XH, Hunkeler EM, et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. JAMA 2002;288:1403–9.
68. Clever SL, Ford DE, Rubenstein LV, et al. Primary care patients' involvement in decision-making is associated with improvement in depression. Med Care 2006;44: 398–40.
69. Loh A, Simon D, Wills CE, et al. The effects of a shared decision-making intervention in primary care of depression: a cluster-randomized controlled trial. Patient Educ Couns 2007;67:324–32.
70. Woolley SB, Fredman L, Goethe JW, et al. Hospital patients' perceptions during treatment and early discontinuation of serotonin selective reuptake inhibitor antidepressants. J Clin Psychopharmacol 2010;30:716–9.
71. Sullivan MD, Katon WJ, Russo JE, et al. Patient beliefs predict response to paroxetine among primary care patients with dysthymia and minor depression. J Am Board Fam Pract 2003;16:22–3.
72. Gutheil TG, Havens LL. The therapeutic alliance: contemporary meanings and confusions. Int J Psychoanal 1979;6(4):467–81.
73. Frank E, Kupfer DJ, Siegel LR. Alliance not compliance: a philosophy of outpatient care. J Clin Psychiatry 1995;56(Suppl 1):11–6 [discussion: 16–7].
74. Ankarberg P, Falkenström F. Treatment of depression with antidepressants is primarily a psychological treatment. Psychother Theor Res Pract Train 2008;45:329–39.
75. Pound P, Britten N, Morgan M, et al. Resisting medicines: a synthesis of qualitative studies of medicine taking. Soc Sci Med 2005;61:133–55.
76. Piguet V, Cedraschi C, Dumont P, et al. Patients' representations of antidepressants: a clue to nonadherence? Clin J Pain 2007;23:669–75.
77. Dulgar-Tulloch L. An assessment of the positive aspects of depression [PhD dissertation]. Albany (NY): State University of New York at Albany; 2009.
78. Van Egmond J, Kummeling I, Balkom TA. Secondary gain as hidden motive for getting psychiatric treatment. Eur Psychiat 2005;20:416–42.
79. Kwan O, Friel J. Clinical relevance of the sick role and secondary gain in the treatment of disability syndromes. Med Hypotheses 2002;59:129–34.

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80. Bogart GT, Ott CA. Abuse of second-generation antipsychotics: what prescribers need to know. Curr Psychiatr 2011;10(5):77–9.
81. Glover E. The therapeutic effect of inexact interpretation: a contribution to the theory of suggestion. Int J Psychoanal 1931;12:397–411.
82. Nevins DB. Psychoanalytic perspectives on the use of medications for mental illness. B Menninger Clin 1990;54:323–39.
83. Gibbons FX, Wright RA. Motivational biases in causal attributions of arousal. J Pers Soc Psychol 1981;40:588–600.
84. Waldinger RJ, Frank AF. Clinicians' experiences in combining medication and psychotherapy in the treatment of borderline patients. Hosp Community Psych 1989; 40:712–8.
85. Swenson CR, Wood MJ. Issues involved in combining drugs with psychotherapy for the borderline inpatient. Psychiatr Clin N Am 1990;13:297–306.
86. Treloar AJ. Effectiveness of education programs in changing clinicians' attitudes toward treating borderline personality disorder. Psychiatr Serv 2009;60:1128–31.
87. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–105.
88. Gutheil TG. The psychology of psychopharmacology. Bull Menninger Clin 1982;46: 321–33.

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