Subjective Effects of Antidepressants

A Pilot Study of the Varieties of Antidepressant-Induced Experiences in Meditators

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Abstract: The use of antidepressants continues to increase, yet relatively little is known about their precise subjective effects, and there is growing concern about subtle psychological side effects. One novel investigative approach to these problems may be to use introspectively trained subjects such as meditators. Experienced meditators recently taking antidepressants rated antidepressant effects on multiple dimensions of experience and reported significant emotional, motivational, and cognitive effects and benefits. This study suggests that a) meditators may benefit both clinically and meditatively from antidepressants, b) meditators may provide significant novel information on antidepressant effects, c) meditators may prove valuable for phenomenological investigations of psychopathology, drug effects, and therapies, d) meditation may prove a helpful maintenance therapy for depression, and e) enhanced equanimity may contribute to the broad therapeutic efficacy of antidepressants.

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In recent years, the use of antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs), has increased dramatically for several reasons. First, the newer antidepressants are considered to have broader clinical efficacy, together with a more benign side-effect profile, lower lethality, and increased social acceptance.

In addition, there is a dramatic reported increase in the incidence and severity of depression, although it is a matter of debate how much of this increase and the apparent increase in certain other disorders is caused by an increase in the actual incidence of depression, and how much to biasing factors such as reduced stigma, better diagnosis, diagnostic creep, and drug industry pressures (Borch-Jacobson, 2002; Shorter, 1997; Torrey and Miller, 2001). Whatever the cause, there can be no argument against the claim, "The impact of major depression on our society cannot be overemphasized" (Jain and Jain, 2002, p 65). These factors and others have contributed to the dramatic rise in antidepressant use, even though recent analyses suggest that the efficacy of SSRIs for depression may be significantly less than formerly believed (Khan et al., 2002; Kirsch and Antonuccio, 2002; Kirsch et al., 2002; Thase, 2002).

There is also growing concern that SSRIs may have previously unrecognized, subtle psychological side effects. These include cognitive deficits, apathy, and a frontal lobe syndrome (Abel et al., 1998; Garland and Baerg, 2001; Hoehn-Saric et al., 1990, 1991; Opler et al., 1994). Likewise, healthy volunteers given SSRIs showed cognitive, attentional, and psychomotor deficits, even though none of the subjects reported difficulties in these areas (Sherman, 2002).

For these reasons, there is growing interest in the precise subjective effects of antidepressants, effects about which we have, as yet, very little detailed information. One way to obtain this kind of information may be to study meditators. Considerable evidence now supports classic claims that meditation practice can enhance introspection and perception, including perceptual sensitivity, discrimination, processing speed, empathy, and concentration. These perceptual changes are also associated with a wide range of psychological, biological, and therapeutic effects (for reviews see Andreasen, 2000; Murphy and Donovan, 1997; Shapiro and Walsh, 1984, 2002; Shapiro et al., 2002; Walsh, 2000; Walsh and Vaughan, 1993; West, 1987). Meditators may therefore give us novel kinds and depths of information about antidepressant effects on cognitive, affective, attentional, and other mental processes.

There are further reasons for studying antidepressant effects on meditators. Meditators often believe that drugs are unspiritual, that their use may impair meditative practice, or that spiritual practice alone should be adequate therapy for

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psychological distress (Epstein, 1993; Victor, 1996). A study of this population may therefore help both meditators and their physicians in deciding whether any of their fears about deleterious effects of medication on practice are justified. This article reports a pilot study of subjective effects of antidepressants on meditators, both in daily life and during meditation retreats.

SUBJECTS AND METHODS

Subjects were recruited through an article in a vipassana meditation magazine, *Inquiring Mind*. Vipassana is a Buddhist meditation that aims at refining awareness, and particularly at systematic, microscopic observation and analysis of all experience, including mental contents and processes (Goldstein, 1983; Goleman, 1988). As such, it seemed a particularly valuable practice for the purpose of this study, identifying subjective mental changes induced by medication.

Criteria listed for participation in the study were a meditation practice of at least 2 years, participation in at least two retreats of a week or longer, and use of antidepressants during the last 2 years. Respondents were mailed a two-part questionnaire. The first part requested information about their medical and psychiatric histories, meditation practice, and effects of antidepressant medications on their daily lives, daily meditation practice, and meditation practice while on retreat. Subjects were asked to provide specific information regarding their type and regularity of meditation practice, years of practice, and time spent in retreat. Regarding antidepressant medication, subjects were asked about the type, dose, and duration of treatment.

The second part of the questionnaire contained 5-point Likert scales for multiple categories of experience. Subjects were asked to rate any changes in these categories of experience, in both daily meditation practice and on retreat, that they attributed to antidepressants. The experiential categories were chosen on the basis of both their clinical and meditative relevance. Clinically relevant categories included, for example, positive emotions such as happiness, joy, and love; negative emotions such as anger, fear, and sadness; energetic factors such as energy/arousal and calm; cognitive capacities such as awareness/clarity and concentration; and imaginal experiences of images and dreams. Experiential categories of particular interest to meditators included several of these and, for example, motivational forces such as attachments and aversions, and emotional factors of compassion and equanimity. Developing the capacity to identify mental experiences and dynamics such as these—to a degree considerably beyond normal—is a central element of Buddhist vipassana meditation training (for an overview of Buddhist psychology and classic texts, see DeSilva, 2000; Nyanaponika, 1998).

Thirteen women and six men (age 22 to 67 years) replied, all of whom had practiced meditation for at least 3 years, most often vipassana. The medications they reported using were Celexa (4; Forest Pharmaceutical, St. Louis, MO), Zoloft (4; Pfizer, New York, NY), Prozac (2; Eli Lilly and Co., Indianapolis, IN), Paxil (2; GlaxoSmithKline, Philadelphia, PA), Remeron (1; Organon Teknika Corp., Durham, NC), Effexor (1; Wyeth-Ayerst Laboratories, Philadelphia, PA), Serzone (1; Bristol-Myers Squibb, Princeton, NJ), and combinations of Trazodone and Serzone (1), Wellbutrin (GlaxoWellcome, Research Triangle Park, NC) and Trazodone (1), Wellbutrin (GlaxoSmithKline, Philadelphia, PA) and Effexor (1), and Wellbutrin and Neurontin (1; Parke-Davis, Morris Plains, NJ).

Statistical Analysis

Subjects were classified according to diagnosis (bipolar or unipolar) and medication type (SSRI, non-SSRI, or mixed). Likert scale scores for daily meditation and for retreat experiences were recorded and analyzed separately.

An optimal approach with multiple measures such as these would be to use multivariate analyses first, but the relatively small number of subjects in this pilot study precluded this approach. Comparisons were therefore based on *t*-tests. There are several ways of handling such multiple measures. A common one, the Bonferroni correction, which divides the usual probability criterion (*e.g.*, .05) by the number of measures, is very conservative, especially for correlated measures, and can significantly increase the risk of type 2 errors (failures to recognize significant effects) (Perneger, 1998; Sankoh et al., 1997). Given the high correlations found among some measures in this study, Bonferroni was judged too conservative, especially for a pilot study such as this. Instead, a conservative criterion of .01 was adopted rather than the more common criterion .05.

No significant differences between the SSRI and other medication groups were found, so these were combined. Likewise, no significant differences were found between the unipolar and bipolar groups—not a surprising finding given that there were only four bipolar subjects—so these were also combined. Subjective effects of medication on daily and retreat meditation experiences were analyzed, and correlations among measures were computed.

RESULTS

Several measures showed significant drug effects at the .01 level (two-tailed), eight in daily meditation and 11 in retreat (Figures 1 and 2; Tables 1 and 2). Of the negative emotions, anger and sadness displayed significant antidepressant-related reductions in retreat, whereas fear was at .011, just below the .01 criterion. However, these effects were not significant in daily meditation. Similarly, all the positive emotions—happiness, joy, love, and compassion—showed significant antidepressant-related enhancement during retreat. The pattern for positive emotions was similar during daily

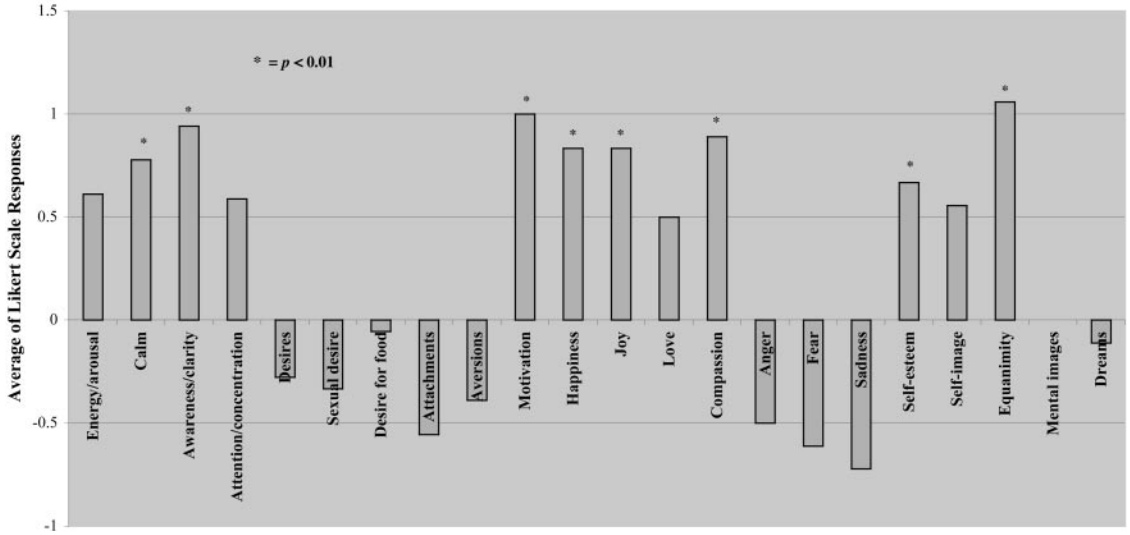

FIGURE 1. Effects of antidepressants during daily meditation.

practice, except that the increase in the experience of love failed to reach the criterion level.

The conative factors of general motivation, general desires, sexual desire, desire for food, attachments, and aversions showed several significant effects. In retreat, general motivation was enhanced, whereas general desires and attachments were reduced. A similar pattern was evident during daily meditation, but the reduction in desire was nonsignificant. For the energetic factors of energy/arousal and calm, only calm evidenced a significant antidepressant effect, enhanced in retreat.

The two cognitive factors awareness/clarity and attention/concentration, which are regarded by meditators as crucial capacities (Goldstein, 1983; Walsh, 1999), appeared enhanced by antidepressants in both daily and retreat meditation, but only awareness/clarity reached the .01 criterion. Self-perception showed an improvement in self-esteem during daily practice, but this failed to reach significance during retreat. Equanimity—a measure of healthy nonreactivity—displayed dramatic and highly significant increases in both daily and retreat practice. However, neither of the imaginal factors of mental images or dreams showed significant ef-

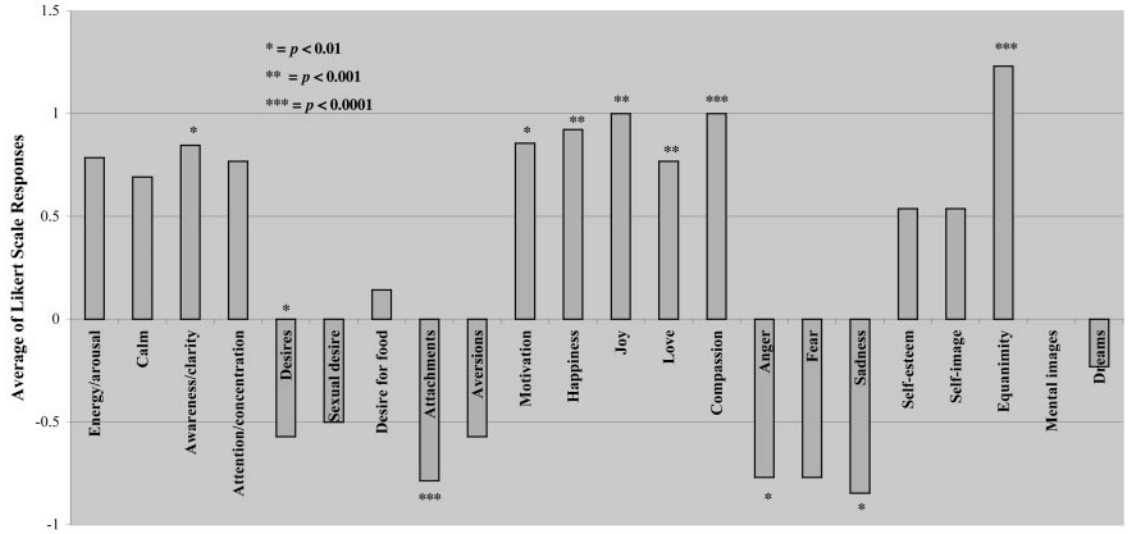

FIGURE 2. Effects of antidepressants during retreat.

TABLE 1. Perceived Effects of Antidepressants During Daily Meditation

	N	M (difference from zero)	SD	t	df	Sig. (2-tailed)
Energy/arousal	18	.61	1.092	2.374	17	.030
Calm	18	.78	1.060	3.112	17	.006
Awareness/clarity	17	.94	1.197	3.241	16	.005
Attention/concentration	17	.59	1.004	2.416	16	.028
Desires	18	–.28	.958	–1.230	17	.236
Sexual desire	18	–.33	1.029	–1.374	17	.187
Desire for food	18	–.06	.873	–.270	17	.790
Attachments	18	–.56	.856	–2.755	17	.014
Aversions	18	–.39	1.037	–1.591	17	.130
Motivation	18	1.00	1.283	3.306	17	.004
Happiness	18	.83	1.043	3.389	17	.003
Joy	18	.83	1.150	3.073	17	.007
Love	18	.50	.924	2.297	17	.035
Compassion	18	.89	1.079	3.496	17	.003
Anger	18	–.50	1.043	–2.034	17	.058
Fear	18	–.61	1.092	–2.374	17	.030
Sadness	18	–.72	1.406	–2.179	17	.044
Self-esteem	18	.67	.970	2.915	17	.010
Self-image	18	.56	.984	2.397	17	.028
Equanimity	17	1.06	1.144	3.816	16	.002
Mental Images	16	.00	.730	.000	15	1.000
Dreams	18	–.11	.900	–.524	17	.607

fects. The SDs of some measures appear high relative to their means, but this is to be expected given that the Likert scales had a range of only 5 units.

DISCUSSION

Taking antidepressant medication was associated with significant effects on multiple dimensions of experience in both daily and retreat meditation. These effects can be usefully examined from clinical and both Western and non-Western theoretical perspectives.

The pattern of emotional responses was as expected from previous clinical studies. The reductions in negative emotions of anger and sadness and the enhancement of positive emotions of happiness, joy, and love are consistent with therapeutic expectations, as are the improvements in calm and self-esteem.

The reported effects can also be examined from a meditative perspective, especially one originating from Buddhist psychology. This was the framework used by the meditators themselves and therefore in part also by the researchers to guide the selection of the experiential categories used in this study. Interestingly, this non-Western perspective also suggests that antidepressant medication was salutary.

Buddhist psychology regards seven mental qualities or capacities—the so-called *seven factors of enlightenment*—as especially crucial to psychological well-being (Walsh, 2000). Four of these factors were investigated here: awareness, calm, equanimity, and concentration. All increased after antidepressant treatment in both retreat and daily practice, but the improvement in concentration reached only .05 significance, not the .01 criterion level.

From the Buddhist psychological perspective, the antidepressant reduction in attachment (craving) is particularly significant, because craving is considered a root cause of suffering and psychopathology. In the emotional sphere, anger, which is regarded as particularly problematic, was reduced, whereas love and compassion, which are especially valued, were both enhanced. From a meditative perspective, this response pattern is a fortunate one (Dalai Lama, 1995).

In short, whether considered from Western or Buddhist psychological perspectives, the changes attributed to antidepressants by the respondents were favorable on multiple experiential dimensions. Observed effects were greater during retreat than in daily practice, as may be expected given that retreats allow for more intense practice and can therefore dramatically enhance introspective sensitivity (Goldstein,

TABLE 2. Perceived Effects of Antidepressants During Retreat

	N	M (difference from zero)	SD	t	df	Sig. (2-tailed)
Energy/arousal	14	.79	1.051	2.797	13	.015
Calm	13	.69	1.032	2.420	12	.032
Awareness/clarity	13	.85	.987	3.091	12	.009
Attention/concentration	13	.77	1.235	2.245	12	.044
Desires	14	–.57	.646	–3.309	13	.006
Sexual desire	14	–.50	1.019	–1.836	13	.089
Desire for food	14	.14	.770	.694	13	.500
Attachments	14	–.79	.579	–5.078	13	.000
Aversions	14	–.57	1.016	–2.104	13	.055
Motivation	14	.86	.864	3.710	13	.003
Happiness	13	.92	.760	4.382	12	.001
Joy	13	1.00	.816	4.416	12	.001
Love	13	.77	.599	4.629	12	.001
Compassion	13	1.00	.577	6.245	12	.000
Anger	13	–.77	.725	–3.825	12	.002
Fear	13	–.77	.927	–2.993	12	.011
Sadness	13	–.85	.987	–3.091	12	.009
Self-esteem	13	.54	.967	2.007	12	.068
Self-image	13	.54	.877	2.214	12	.047
Equanimity	13	1.23	.725	6.121	12	.000
Mental images	12	.00	1.044	.000	11	1.000
Dreams	13	–.23	.725	–1.148	12	.273

1983). The measurement of these multiple dimensions in meditators revealed a richer pattern of antidepressant-related responses than has been obtained in previous studies, a pattern that, as discussed below, has both theoretical and clinical implications.

Limitations of This Study

Of course, these and other conclusions should be qualified by the limitations of this study. These limitations include the fact that the subject population was small, heterogeneous, and self-selected; that the subjects were not all taking the same medication; that the experimental design was not controlled or blind; and that the measures were introspective self-reports.

Introspection as a research tool has been inconsistently valued, depending on the orientation of researchers. It was central to early experimental psychology and diverse psychotherapies, although it was anathema to behaviorism, made a limited return at the microanalytic level in cognitive psychology, and is viewed as essential to consciousness studies and integral research approaches (Varela and Shear, 1999; Wallace, 2000; Wilber, 2000).

In Asian psychologies, such as Buddhist and yogic systems, introspection is crucial, and these psychologies stem from and are designed to foster refined introspective capacities. In this, they would claim to be effective, and certain of their claims are now supported by laboratory research (Murphy and Donovan, 1997; Shapiro and Walsh, 2002).

The fact that most of the measures obtained in this study, including all of the retreat measures, were retrospective is a limitation, and future studies may wish to use meditation logs rather than, or in addition to, retrospective assessments. The sample size is obviously small considering the large number of measures examined. As discussed, we attempted to correct for this by adopting a conservative significance criterion of .01. Confounding biasing factors such as expectancy and social approval are possible concerns. However, positive response biases may have been less than in most patient populations because of the negative ways medications are often viewed by meditators.

Finally, the heterogeneous, self-selected patient population is a limitation, and future studies may benefit from more rigid selection criteria. However, a heterogeneous population such as this does have some benefits. The gold standard for evaluating clinical effects is the randomized controlled trial (RCT) using highly selected, homogenous patient samples. However, there is increasing concern about the limits of

RCTs. Exclusion rates are high, and outcome success is a function of the stringency of exclusion (Westen and Morrison, 2001). An unfortunate result of using these homogenous populations is therefore that "very little is known about whether the results of RCTs generalize to the patients seen in routine clinical practice" (Persons, 1998, p 80).

On the positive side, as a pilot study, this investigation seems to have yielded fruitful findings. Specifically, it seems to have a) demonstrated the feasibility of using an introspectively trained population to obtain an unprecedented variety of information on subjective effects attributed to antidepressants, b) examined the responses of meditators to antidepressants, c) tested whether meditators perceived their meditative practice to be harmed (as many of them feared would happen) or helped (as proved to be the case), and d) demonstrated the feasibility of obtaining subjective measures of both clinical and contemplative relevance and of drawing connections between them.

Novel Implications of This Study

This study suggests a number of novel implications. These include the value of using supersensitive subjects in pharmacological and other studies to provide rich phenomenological information about psychopathology, drug effects, and psychological processes. The study also suggests therapeutic implications, insights into certain psychological processes, a possible mechanism of antidepressant action, and the possibility of meditation as a maintenance therapy for depression. Finally, it allays the widespread fears among meditators and other contemplative practitioners that antidepressants may prove harmful to their practice.

Supersensitive Subjects and Phenomenological Mapping

This study and a variety of other sources suggest that meditators, as supersensitive subjects, may be able to detect and discriminate multiple dimensions of experience often overlooked or conflated by patients or normal subjects. This suggests using supersensitive subjects to explore in novel ways the phenomenology and experiential structure of diverse phenomena, such as psychological processes and dynamics, and clinical psychopathologies, drug effects, and therapeutic interventions.

Psychopathologies are experienced as specific states of mind. By using supersensitive subjects, it may be feasible to develop phenomenological maps—multidimensional, experiential profiles—of specific psychopathologies, and of experiential effects of specific drugs and psychotherapeutic interventions, and to compare effects of different interventions (Walsh and Vaughan, 1993). Comparisons of the patterns of depressive symptom change after cognitive or pharmacological therapy using subjects untrained in introspection have produced preliminary findings of intriguing differences (Imber et al., 1990; Reda et al., 1985; Rush et al., 1981). Perhaps supersensitive subjects can provide additional, and more precise, information.

Of course, introspection fared poorly as a research tool in early Western psychology, but one reason may be that, by meditative standards, subjects received extremely little training (Walsh, 2000). Highly trained, supersensitive subjects may be another matter.

Psychological Mechanisms of Antidepressant Action

One of the most striking characteristics of many antidepressants, and especially SSRIs, is their remarkable and growing range of clinical applications. This has led to a conceptual conundrum: how do they do this, and what mechanisms of action could possibly explain their dizzying array of applications? The current study suggests one possible answer: equanimity.

Equanimity may be defined as the capacity to experience potentially provocative stimuli fully and nondefensively with minimal psychological disturbance. As such, it is a healthy capacity, and one that must be differentiated from unhealthy counterfeits such as indifference, apathy, anhedonia, dyslexithymia, rigid control, or even conscious masking. Buddhist psychology regards counterfeits such as these as unhealthy "near enemies" of equanimity—that is, unhealthy psychological qualities that can be mistaken for equanimity (Longchenpa, 1975).

The mental quality of equanimity is little recognized in Western psychology and psychiatry; there is, for example, no entry on it in the *Encyclopedia of Psychology* (Corsini, 1994). Perhaps the closest well known analogue is the psychoanalyst Elizabeth Zetzel's (1970) concept of "affect tolerance," which she believed was essential for emotional growth, and which Richard Schwartz (1991, p 400) defined as the capacity "to stand to feel what you feel." Peter Kramer (1993, p 258) suggests the closely related concepts of "emotional resilience" and "experience-tolerance."

Equanimity is highly and widely valued across a remarkably diverse range of contemplative disciplines, psychologies, and philosophies. In philosophy, it was praised as the *apatheia* or *euthymia* of Stoicism, the *ataraxia* of Epicureanism, the "principle of the equality of things" of Taoism, and the "vision of sameness" of Indian Vedanta (Hallie, 1967; Walsh, 1999). Among contemplative disciplines, it underlies the "contented self" of Sufism, the "divine apathea" of the Christian Desert Fathers, *Hishtavut* in Judaism, *masatva* in Jainism, *vairaga* in yoga, and equanimity in Buddhism (Fadiman and Frager, 1997; Feuerstein, 1990; Longchenpa, 1975; Walsh, 1999, 2000).

Buddhist psychology offers a particularly detailed examination of equanimity. Here it is regarded as crucial to the development of peace, mental well-being, and maturity. Its

role is to stabilize and immunize the mind against perturbations. Most importantly, it is regarded as a mental potential that can be cultivated through meditation and other contemplative practices, a potential that is virtually unrecognized in Western psychology (Kornfield, 1993; Longchenpa, 1975).

Could the wide-ranging effectiveness of antidepressants, and perhaps particularly SSRIs, be caused in part by a mechanism of action that enhances equanimity? Certainly findings from the present study suggest this possibility. The most striking of all the reported drug effects was an increase in equanimity. Moreover, this increase showed high correlations with other positive mental capacities such as awareness/clarity ($r = .78$, $p < .001$), calm ($r = .78$, $p < .001$), concentration ($r = .67$, $p < .005$), and compassion ($r = .71$, $p < .001$). It also showed significant negative correlations with the problematic mental qualities of attachments ($r = -.72$, $p < .001$) and sadness ($r = .83$, $p < .001$; all correlations from daily meditations).

Actually, the mechanism of equanimity has already been hinted at in the psychiatric literature, although not precisely recognized and articulated. Several reports suggest an inverse relationship between indices of central serotonin function on the one hand and measures of impulsivity and aggression on the other (Coccaro et al., 1997; Manuck et al., 1998). Peter Kramer (1993, p 134) raises the possibility of "serotonin as police," implying that serotonin may be involved in multiple disorders because it sets affective tone. He also suggests that Prozac may increase emotional resilience, experience tolerance, and affect tolerance, terms he uses more or less synonymously.

Likewise, Simon Sobo (1999, p 23) suggests that SSRIs may be so widely efficacious because of a similar nonspecific effect: "The most frequent description that I have heard from my patients of the effects of SSRIs is an attitude of 'it doesn't matter' or 'don't sweat the small stuff' or 'what's the big deal?'" He therefore describes SSRIs as "well, whatever" medications. All these findings and suggestions seem consistent with the idea that a psychological mechanism of antidepressant, and particularly SSRI, effectiveness may be through enhancing equanimity.

Equanimity may also account for the apparent contrast between the facilitation of joy and love found in this study and a case report of sertraline suppression of exceptionally intense levels of these two emotions in a meditator performing specific practices to elicit these emotions strongly (Walsh et al., 2003). This contrast is consistent with the idea that certain antidepressants may facilitate, or remove depression-associated blocks to, normal levels of positive emotions such as love and joy, but inhibit unusually intense experiences.

Meditation as Maintenance Therapy

The mechanism of equanimity is also consistent with the idea that meditation, which fosters equanimity, may help stabilize therapeutic gains initially produced by medication. Such was the suggestion of two respondents in this study who spontaneously reported that meditation eventually replaced drugs, leaving emotional stability intact. As one respondent stated, "medication allowed me to get a grip on mental health," which she then felt able to maintain with meditation. Obviously, these claims need to be accepted cautiously. There were no controls, the subjects had been in drug-free remission for less than a year, and relapse risk is a function of duration of the drug-free interval. On the other hand, these claims may be part of an emerging larger picture of the efficacy of psychological treatments for relapse prevention.

Depression is increasingly recognized as a long-term, relapsing condition. Consequently, relapse prevention is becoming a greater focus, and long-term pharmacotherapy is becoming the norm. However, considerable data suggest that relatively brief psychotherapy—cognitive therapy has been the most researched—may be as effective, or even more effective, in relapse prevention (Beck and Weishaar, 2000; Fava et al., 1998; Garland and Scott, 2002). A similar pattern is emerging for panic disorder (Bruce et al., 1999) and even more dramatically in obsessive-compulsive disorder, for which behavior therapy is several times more effective than pharmacotherapy in preventing relapse (Foa and Kozak, 1996; Kaplan and Greist, 2002). Therefore, it would not be surprising if meditation—especially long-term, daily practice—could facilitate relapse prevention and health maintenance, especially because the combination of meditation and cognitive therapy has already proven helpful in this regard (Segal et al., 2002). Certainly, the possibility that meditation may reduce relapse warrants investigation.

CONCLUSION

The results of this study suggest that a) meditators may benefit both clinically and meditatively from antidepressants; b) meditators may provide significant novel information on antidepressant effects; c) meditators may prove valuable for phenomenological investigations of psychopathology, drug effects, and therapies; d) meditation may prove a helpful maintenance therapy for depression; and e) enhanced equanimity may contribute to the broad therapeutic efficacy of antidepressants.

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