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**The Controversy Over Antidepressant Drugs in an Era of  
Evidence-Based Practice**

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### **Abstract**

Questions regarding the efficacy of antidepressant drugs has been a recent focus of attention in the national news both in print and in the television media. Many clients will have questions regarding what they can believe and how they can address mood problems. Social workers constitute a greater percentage of the mental health work force than any other profession. Thus, social workers will probably be asked by clients about these issues. This paper presents information on the efficacy of antidepressants for both the short and long term. It covers adverse effects and withdrawal symptoms. Clients' self-determination should be honored. However, social workers can be of assistance in supplying facts relevant to decision making.

## **The Controversy Over Antidepressant Drugs in an Era of Evidence-Based Practice**

During the last year, anti-depressants have been a point of focus in the national news. On February 19, 2012, Lesley Stahl's interviewed Irving Kirsch on *60 Minutes*. Kirsch reported on his analysis of data reported to the FDA by the pharmaceutical houses on the eight week efficacy of antidepressants. For individuals with mild and moderate depression, antidepressants are no more effective than placebo. Prior to the CBS broadcast, in the summer of 2011, Marcia Angell, the former editor of the *New England Journal of Medicine*, contributed a review of Robert Whitaker's *Anatomy of an Epidemic* to *New York Review of Books*. Whitaker (2010) contrasted the long term efficacy of treatment for bipolar, major depression, and schizophrenia with outcomes before the availability of drugs. Whitaker concluded that outcomes have worsened with the availability of drugs and speculated on psychotropic medications as a contributing factor to the swelling Social Security Disability rolls in the United States. A sharp debate ensued between several psychiatrists and Marcia Angell which was covered by the *New York Times*.

Stoesz (2012) recently reviewed the same trio of books in *Research in Social Work Practice*, arguing the importance of these issues within social work. Social workers constitute 65% of the workforce providing mental health services in the United States (Cohen, 2003; Mechanic, 2008). Moreover, 35% of social workers designate "mental health" as their primary area of service (NASW Center for Workforce Studies, 2008). Major depression is a disorder with high prevalence in the general population (Kessler et al., 2005; Moffitt et al., 2009) and presently 11% of the general population over age 12 is taking an antidepressant. Over 60% of persons taking antidepressants have been taking them for two years or longer, with 14% having taken them for over a decade (Pratt, Brody, & Gu, 2011). Survey research suggests that social

workers are involved with the issue of psychotropic medications (Bentley, Walsh, & Farmer, 2005).

### **Outcomes from the Short Term Drug Trials**

Over half of the outcome studies submitted to the FDA found that antidepressants do not produce effects that are significantly better than placebo in reducing symptoms of depression as assessed by the 51 point Hamilton rating scale (Kirsch, 2010, p. 46). The widespread impression that antidepressants are more effective than this is largely driven by the fact that pharmaceutical companies have generally only published the positive studies, thus distorting the peer-reviewed literature (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). To work around the confound of selective reporting, Kirsch obtained all of the studies submitted to the FDA by the pharmaceutical houses. In his analysis of all the studies, the difference between the placebo and antidepressant conditions of the study was only 1.8 points out of 51 (p. 28). In some of the studies, patients had completed ratings of their side effects. After controlling for the difference in perception of side effects, the difference between the group on antidepressants and the group on placebo was no longer significant, suggesting that the improved outcomes were totally attributable to the expectancy effects induced by the stronger side effects of the actual drug. Indeed, in studies where atropine is employed as the placebo so patients are more likely to believe they are taking a real drug, only 2 of the 9 studies showed superiority of antidepressant over placebo.

In the Stahl interview, it was reported that for those who are severely depressed, defined as those with Hamilton rating scale scores above 28 points, antidepressants are effective. This result was replicated in meta-analyses of [the FDA studies](#) by Fournier et al., (2010) and Khan, Leventhal, Khan, & Brown (2002). Even among the severely depressed, however, there is only a

four point difference on the Hamilton Rating Scale between the drug treated and the antidepressant group (Kirsch, 2010, p. 33).

The psychiatric establishment is clearly aware of the problems with the efficacy of antidepressants, and there have been some counter-arguments made. There has been quibbling in the literature about the meaning of the small difference between drug and placebo groups. Kirsch has found a difference of 1.8 points, but others research teams argue that the true difference is 2.18-2.68 (Fountoulakis & Möller, 2011). In terms of clinical, real-world significance, there seems to be little difference between the various findings. The HAM-D has been critiqued as an outcome measure, but, this was chosen by the pharmaceutical companies, and other data (such as Quality-of-Life scales) that would be more relevant to functional recovery have been collected but generally not published (Healy, 1997).

Many clinicians have also remarked that they see clients getting better on antidepressants, so these results are difficult to believe. Kirsch (2010) agrees with this point to a degree; patients do get better, on antidepressants and on placebos. Importantly, receiving a placebo in a clinical trial is not *nothing*; it includes close monitoring and non-specific psychosocial helping from a helping professional. The question is not whether antidepressants do something- they clearly do- but the degree to which they are essential for recovery. In an era of evidence-based practice, to insist that antidepressants work on the basis of anecdote would seem strange indeed.

A similar critique is that randomized controlled trials (RCT) of antidepressants do not mimic real-world psychiatric practice. Thus, the STAR\*D study, a \$35 million dollar NIMH-funded depression study, is all the more important. This study was less selective in the types of depressed clients recruited for the study. Clients were randomized to various “real-world” treatments for depression, and allowed augmentation and other psychopharmacological strategies

not usually allowed in RCTs. The study resulted in a slew of publications, confusing interpretation, but one of the principal investigators summarized the results by writing, “the proportion that responded or remitted and stayed well for a year was estimated to be a disappointing 15%” (Nierenberg et al., 2008, p. 433).

Michael Thase, an industry funded psychiatry researcher, appeared on the *60 Minutes* segment defending antidepressant efficacy. In *Psychiatric Times*, Thase (2002), **debating with Kirsch in print**, acknowledges that only one to two very-depressed persons of every 10 prescribed an SSRI get a “substantial benefit,” but argues that from a public health perspective, that means many people are being helped. It is further acknowledged that only 2/3 of patients in eight week drug trials achieve a 50% reduction in their symptoms (Thase et al., 2005; Tranter, O’Donovan, Chandarana, & Kennedy, 2002). **Only 40% of patients on active drug achieve remission during the eight week trial according to both Nemeroff, another recognized expert in the field of treatment of Major Depression (2011) and Thase et al. (2005).** According to **DeRubeis, Fournier, and Fawcett (2010) examining data from the National Institute of Mental Health Collaborative Depression Study, the remission rates broken down by disease severity are:** for very severe, 32% on drug versus 18% on placebo; for severe group, 34% on drug versus 27% on placebo; for mild and moderate, 45% on drug versus 44% on placebo. Indeed, Tom Insel (2009), Director of the National Institute of Mental Health has acknowledged, “The unfortunate reality is that current medications help too few people to get better and very few people to get well” (p. 704).

When following patients longitudinally, asking whether antidepressants increase the numbers expected to achieve remission from an episode, there is not much opportunity for antidepressants to yield superior results. The rate of recovery from a bout of depression without

any treatment of any kind is high. Estimate of the duration of an episode of depression before the advent of drugs was an average of six to eight months (Beck, 1967, p. 51; Coryell et al., 1994; Klein, Gittelman, Quitkin, & Rifkin, 1980 p. 410; Lehmann, 1983). Reports suggested that 80% of patients without any treatment will recover within two years (Lehmann, 1983; Coryell et al., 1994; Spijker et al., 2002). These figures are the consistent with the findings of the

The National Institute of Mental Health Collaborative Depression Study which also found that the duration of an episode remains relatively constant at about 20 weeks regardless of the number of previous episodes and the probability of recovery from an episode remains high regardless (88-92%) of the number of previous episodes (Solomon, Keller, Leon, Mueller, Shea, Warshaw, Maser, Coryell, & Endicott, 1997). Several studies allow for examining how medications alter the duration of an episode of depression. In a naturalistic study by Brugha, Bebbington, McCarthy, Stuart, and Wykes (1992) following patients out 3 to 6 months, the recovery rate for the high-dosage medicated group was 70% and for the unmedicated group was 71%. The difference was not statistically significant. In another naturalistic study by Ronalds, Creed, Stone, Webb, and Tomenson (1997) recovery rates were better in the unmedicated than in the medicated group. Longer time to recovery in those on medications was the case in Coryell et al.'s (1994) study of the National Institute of Mental Health Collaborative Depression Study. Coryell et al. speculated that the treated group may not have sought treatment until their symptoms had persisted for a protracted interval, thus accounting for the longer episode duration in the medicated group.

### **Prevention of Relapse**



The drug company studies of antidepressants efficacy examine response rates at eight weeks. Most people are not interested in temporary reprieve but rather want sustained recovery. Here, the duration of wellness between episodes of depression is what counts. In the pre-drug literature, Lehmann (1983) indicates that most individuals experienced remission for two to three years. Zis and Goodwin (1979) reviewing early studies found that between 57 to 66% did not experience a second episode.

There is now a body of literature studying relapse rates among those prescribed antidepressants. In a meta-analysis of those who continued on drug, Williams, Simpson, Simpson, and Nahas (2009) report that 23% will relapse by one year, 34% relapse by two years, and 45% relapse by three years. Keller et al. (2007) looked at relapse rates for individuals who had experienced at least two episodes of depression prior to entry into their study. They followed those who responded during the initial ten weeks of treatment for six months. By six months, 19% had relapsed. Those with sustained remission at six months were followed out for an additional two years. By two years, another 19% had relapsed.

There are also a series of naturalistic studies that examined relapse rates in those continuing on drugs versus those who were unmedicated or medicated in fewer of the follow-up weeks. This contrast might be biased against the medicated group; it is known that people with more extreme symptoms are more likely to seek treatment (Leon et al., 2003). Judd et al. (2000) followed patients from the National Institute of Mental Health for Collaboration Program for 9 years. Those with residual symptoms were medicated for 50.9% of weeks in contrast to 38.4% of weeks for those without symptoms (Judd et al., 1998). Of those with residual symptoms at the beginning of the study, 92.3% had relapsed within the 9 years and 65.7% without residual symptoms had relapsed (Judd et al., 2000). In several naturalistic studies differences in relapse

rates in those who were and were not on drug were not significant (Judd et al., 2000; Mueller, Leon, Keller, et al., 1999). Hughes and Cohen (2009) conducted a literature search of the long term outcomes of at least ten years from depression, which included some of the aforementioned studies. Some of the studies were of medicated individuals whereas several studies were of unmedicated individuals. Hughes and Cohen concluded that outcomes for the medicated did not differ from the non-medicated.

A study by Bockting et al. (2008) found that the continuous users did not differ from the non-users in terms of demographics, residual symptoms, or number of previous episodes. In the Bockting, et al. (2008) study those who did not take antidepressants after their last recovery from a depressive episode were less likely to relapse (60% relapse in the continuous users versus 46% in the non-users over the two year period).

### **Drug Discontinuation Studies**

A number of studies have selected those patients who recovered from an episode of major depression on drug and then switched half to placebo, sometimes without any tapering of medications, while others continued on drug. According to reviewers of these studies (Andrews et al., 2011; Geddes et al., 2003; Littrell, 1994), a consistent finding in these studies is that approximately 42% of the patients switched to placebo relapse which is a much higher rate of relapse contrasted with those who remain on drug. Some have interpreted these data as evidence of a continued need for antidepressant treatment to stem the natural course of depression. However, the duration of remission varied across studies, but the high rate of relapse (sometimes with 70% relapsing) always occurred within the six months of drug discontinuation. Indeed, rates of remission far exceeded the numbers who were expected to never experience a second episode of depression suggested in the pre-drug literature. The timing of remission was pegged to the

time of drug discontinuation rather than the duration of the wellness interval. It has been argued that the high rate of depressive symptoms probably reflects drug withdrawal (Littrell, 1994) although Andrews et al. (2011) argued that drugs alter the brain in such a way that relapse is more likely.

*Examining data using hierarchical linear modeling with covariates.* An analyses of the NIMH Collaborative Depression Study has been published in which variables predicting greater likelihood of receiving high dose medications were controlled, viz. more severe symptoms and a greater number of previous episodes (Leon et al., 2003). In this analysis, each research participant had multiple observation periods during which the impact of medication status (no medications, low dose, moderate dose, and high dose) was evaluated. That is, after a research-participant recovered from an episode, she/he was entered into a new trial period to examine time to a second relapse. Leon, Hedeker, and Teres (2007) reported that those on high dose medications were less likely to relapse. The problem with the analysis is that at the initiation of each period, research-participants were not evaluated for previous medication status prior to the initiation of a trial. If a research-participant was taken off medications at the beginning of a trial while others continued on a medication, then depression relapse in those not receiving medication might reflect drug withdrawal as opposed to a beneficial effect of the medication. The findings from this analysis are thus impossible to interpret.

### **What to Conclude about Prevention of Relapse?**

The proper way to evaluate the efficacy of drugs for prevention of relapse is to have random assignment to placebo arm versus drug treatment and then follow for many years afterwards. There are no such studies. In absence of that, we have naturalistic studies. Inferences on drug efficacy suffer because the sample “not on drug” may include who were once

on drug but then discontinued their drug. They may relapse, not because they were deprived of an effective drug, but rather drug discontinuation is associated with withdrawal. Additionally, in the naturalistic studies, comparing those without treatment to those with treatment may not compare the same type of individuals. Those with more severe depression are more likely to seek treatment (Leon et al., 2003). We also have studies of those that are treated continuously on drugs. We can compare relapse rates in the continuously treated to pre-drug relapse rates. However, this type of comparison is not as good as comparisons of those who are randomized. Times have changed since the pre-drug world, and other factors may be at play which might explain the higher rate of relapse current than was found in the pre-drug world. Whitaker's (2010) book *Anatomy of an Epidemic* contrasts pre-drug outcomes with currently reported outcomes. Whitaker and others have speculated that antidepressants might worsen the course of depression and contribute to chronicity (Byrne & Rothchild, 1998; Fava & Offandini, 2011). Unfortunately, the question of whether antidepressant drugs worsen the long term course of major depression has not been asked with a legitimate design. What can be gleaned from the naturalistic studies and the studies examining relapse rates on drugs compared to outcomes pre-drug is that there is no evidence that antidepressants improve outcomes.

### **Response to Lack of Efficacy**

Psychiatrists are aware that antidepressants lack efficacy. Several antipsychotic drugs are licensed for treatment-resistant depression; there is a growing movement to add an antipsychotic to the regimen of the large number of patients who do not respond impressively to a selective serotonin reuptake inhibitor (SSRI). Indeed, atypical antipsychotics have been approved by the FDA for individuals who fail to respond to their antidepressants. The problem with the atypicals is that they result in brain volume reduction (Ho, Andreasen, Ziebell, Pierson, & Magnotta,

2011) which animal work suggest occurs when taken over a two year period (Konopaske et al., 2007, 2008). Additionally, the atypicals induce weight gain which fails to plateau, dyslipidemia, and diabetes (McIntyre, McCann, & Kennedy, 2001). Although the atypicals are not as likely to induce movement disorders as the older drugs, they are associated with motor problems (Casey, 2006; Manschrek & Boshers, 2007; Miller et al., 2005). The FDA has warned that the atypicals are associated with fatal heart arrhythmias (Psychiatric News Alert, 2011).

### **Adverse Effects Short Term**

The adverse effects of antidepressants are often clinically important. The merely annoying side effects include nausea and dry mouth (PDR, 2012). Other effects are more concerning. Rosen, Lane, and Menza (1999) report that 80% of persons taking an SSRI will experience sexual dysfunction which includes anorgasmia, erectile dysfunction, diminished libido, and genital anesthesia. Csoka, Bahrack & Mehtonen (2008) report that sexual dysfunction can continue even after drugs are discontinued. Serotonin transporters, the target for the SSRIs, are also found on blood platelets and SSRIs are associated with risk of bleeding ulcers (Loke, Trivedi, and Singh, 2008; Serebruany, 2006) and stroke (Wu, Wang, Cheng, & Gau, 2011). Serotonin transporters are found on cells involved in bone turnover and SSRIs increase the risk for osteoporosis (Bliziotis, 2010; Kawai & Rosen, 2010). SSRIs can also induce movement disorders including lip-smacking and dystonia (Leo, 1996; Zhou et al., 2005) and cognitive dysfunction (Fava, 2006; Damsa, et al., 2004).

There is a substantial literature questioning whether antidepressants in some way interfere with whatever mechanism the body might have in maintaining neutral mood. Antidepressants can induce mania (Leverich, et al., 2006; Post, Denicoff, & Leverich, 1997), violence (Moore, Glenmullen, & Furberg, 2010), and suicidal ideation (Laje et al., 2007).

Reports of emotional numbing with antidepressants are found in the literature. In order to verify reports of emotional numbing, McCabe, Mishor, Cowen, and Harmer (2010) conducted functional magnetic resonance imaging study of healthy individuals who had taken citalopram for seven days. Diminished response to both positive and negative stimuli was observed on the imaging.

On a more serious note, SSRIs are also associated with the Selective Serotonin Syndrome captured by tremor and muscular rigidity, high temperature, mental clouding or agitation, rapid heart-beat, and increased blood pressure. The condition can be lethal (Boyer, & Shannon, 2005).

### **Adverse Effects Long Term**

Psychiatrists are currently acknowledging that major depression cannot be explained by any simple deficit of any particular neurotransmitter (Lacasse & Leo, 2006). However, the new view is that depression is actually caused by systemic inflammation which then influences the brain (Raison, Capuron, & Miller, 2006). Ironically, there is much evidence that while eight weeks of antidepressants will decrease inflammation (Kubera et al., 2011; Maes et al. 2011), the opposite occurs when these drugs are taken over a two year period. Metabolic syndrome and obesity are associated with systemic inflammation. SSRIs increase the risk of weight gain and metabolic syndrome (Dannon et al., 2007; Fava, 2000; Kivimäjum et al., 2010; Raeder, Bjelland, Vollset, & Steen, 2006; Serreti & Mandelli, 2010). Type II diabetes is considered an inflammatory condition and SSRIS increase the risk of Type II diabetes (Andersohn, Schade, Suissa, & Garbe, 2009; Kivimäjum et al., 2010; Rubin et al., 2010). Long term antidepressants increase inflammatory markers such as CRP (Hamer et al., 2011), a predictor of heart attacks. Long term antidepressants are associated with diminished heart rate variability (Dawood et al.,

2007; Kemp et al., 2010; Licht et al., 2008), another predictor of cardiovascular disease and heart attacks.

### **Drug Withdrawal**

For those opting to discontinue antidepressant medications, drug withdrawal constitutes a significant obstacle. Withdrawal symptoms include dizziness, nausea, lethargy, headache, anxiety, tingling and burning sensations, confusion, tremor, sweating, insomnia, irritability, memory problems, anorexia (Haddad, 1997). Others have reported muscle spasms and protruding tongue movements (Ceccherini-Nelli, Bardellini, Cur, Guazzelli, Maggini, & Dilsaver, 1993; Stoukides & Stoukides, 1991). The emergence of mania and hypomania has also been reported (Goldstein, Frye, et al., 1999; Lejoyeux & Adéx, 1997; McGrath, Stewart, Tricamo, Nunes, & Quitkin, 1993). Even in those taking depression for anxiety who were not initially depressed, depression emerges as a component of withdrawal (Pato, Zohar-Kadouch, Zohar, & Murphy, 1988).

Unfortunately, little is known regarding the duration of drug exposure required to induce withdrawal or the percentages that are estimated to experience withdrawal as a function of dosage of exposure. Haddad (1997) has reported that an eight-week exposure is required to witness drug withdrawal and estimates vary widely (between 20 to 86%) as to the proportion that will exhibit withdrawal symptoms. The psychiatric literature fails to provide protocols for withdrawing patients. However, Joseph Glenmullen (2005) has provided instructions on how to taper drugs which might guide the physician. A study by Frank, Kupfer, and Perel (1989) suggests that psychotherapy during the drug withdrawal is protective in preventing relapse.

### **Concerns about Pregnancy**

Antidepressants are associated with increased risk of autism in the baby (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011). Antidepressants consumed during gestation are associated with heart malformations in the baby and problems in establishing proper lung function after birth (Chambers et al., 2006; Gentile, 2011; Udechuku, Nguyen, Hill, & Szego, 2010).

## **Alternatives**

### **Psychotherapy**

In studies in which Cognitive Behavior Therapy (CBT) is contrasted with antidepressants, antidepressants sometimes achieve response rates faster, but by the end of the study outcomes equalize (Blackburn & Moore, 1997; Elkin et al., 1989; Shea et al., 1992; Simons, Murphy, Levine, & Wetzel, 1986; Watkins et al., 1993). A meta-analysis examining comparative efficacy of CBT versus drugs for the severely depressed found no difference in efficacy, although effect sizes were greater for the CBT group (DeRubeis, Gelfand, Tang, Simons, 1999). A large study conducted by Keller et al. (2000) found that a combination of drug and psychotherapy achieved better results than either treatment alone. After treatment discontinuation in those treated with either drug or CBT, those treated with talk therapy show lower rates of relapse (Evans et al., 1992; Simons et al., 1986). Moreover, talk therapy during the follow-up interval also decreases relapse among those who are not medicated (Bockting et al., 2008).

### **Exercise and Diet**

In the clinical literature exercise has demonstrated efficacy in ameliorating major depression (Hoffman et al., 2011) with effect sizes comparable to pharmacological interventions (Greenwood & Fleshner, 2008). Moreover, omega-three fatty acids are associated with lower risk of major depression and have been proven to reduce distress among those under stress



(Kiecolt-Glaser, 2010; Kiecolt-Glaser, Belury, Andridge, Malarkey, & Glaser, 2011).

Mediterranean diets are associated with lower cytokine levels, less oxidative stress, and lower levels of depression (Dai et al., 2008; Sanchez-Villegas et al., 2009). Thus, many non-drug alternatives for treating depression are available.

### **What to Do?**

This look at the antidepressant literature contradicts some of the beliefs promoted by the pharmaceutical industry (Gomory, Cohen, Wong, & Lacasse, 2011). In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) issued new guidelines in October of 2009 (NICE, 2009) based on their review of the antidepressant outcome data. These guidelines represent a substantially different approach to depression than the U.S. system. The NICE guidelines recommend a stepped-care approach whereby watchful waiting, psychosocial approaches and self-help strategies are emphasized rather than medication for those with mild to moderate depression. In an era of evidence-based practice, it is important to note that the United Kingdom (a country with many similarities to our own) has looked at the research evidence and reached an “evidence-based” decision that SSRIs should not be prescribed casually, and that given the risk-benefit ratio, alternative approaches should be trialed before resorting to an SSRI.

Professional organizations have failed to specify particular duties that mental health professionals who are not physicians have with regard to medications. However, in a well-publicized case (*Osheroff v. Chestnut Lodge*) a treatment facility was successfully sued for failing to discuss the medication option in treating a patient’s depression. The NASW Code of Ethics does require obtaining informed consent and some legal scholars contend that this requires discussion of proposed treatments as well as the range of other treatments that are available (Littrell & Ashford, 1994). Offering clients evidence-based information on the short-term and

long-term efficacy as well as the adverse effects may be an important component of obtaining informed consent, although state licensing laws should be consulted as well. Some clients will opt to take a medication and our profession is committed to self-determination. Our job is not to make decisions for clients, but rather to ensure that they are fully informed. The information provided here may be useful in fulfilling this informed consent obligation.

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