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Recommended Citation
Littrell, Jill, "Is there Evidence for the Bipolar Spectrum and the Safety of Pharmaceutical Interventions?" (2012). *Social Work Faculty Publications.* Paper 35.
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Is there Evidence for the Bipolar Spectrum and the Safety of Pharmaceutical Interventions?

Abstract

Social workers constitute a high proportion of mental health professionals and a high percentage of social workers provide mental health care. Thus, psychiatric diagnoses and pharmaceutical interventions are relevant for many social workers. This paper reviews the rise in the diagnoses of Bipolar spectrum disorders for both children and adults. It considers the safety of antipsychotic medications, a mainstay of treatment for children and adults, which, in addition to other well-documented negative side effects, have recently been shown to decrease brain volume by a significant percent. These issues are particularly relevant for children in the foster care system.

Key Words: Evidence-based practice; Bipolar Disorder; Social Workers in Mental Health; antipsychotic medications

Is there Evidence for the Bipolar Spectrum and the Safety of Pharmaceutical Interventions?

Social workers provide as much as 65% of mental health services in this country (Cohen, 2003; Mechanic, 2008) and 35% of social workers identify mental health as their area of practice (NASW Center for Workforce Studies, 2008). Moreover, professional social workers are major players in Child Welfare system and in provision of mental health treatment to low income children. Articles in favor of evidence-based practice have appeared in the literature (Satterfield, et al., 2009; Thyer, 2004). Evidence-based practice requires that there is empirical support for the legitimacy and constructive value of diagnostic categories. Similarly, treatments must have passed muster within the empirical literature for both effectiveness and safety. The purpose of this paper is to examine the constructive value of Bipolar Spectrum diagnoses and the safety and efficacy of pharmacological treatments.

The last decade has witnessed a huge rise in bipolar diagnoses both for children and adults. While in 1996, pediatric bipolar was the least frequent diagnosis for hospitalized children; by 2004, it was the most frequent diagnosis (Blader & Carlson, 2007). More specifically, within eight years the diagnosis for children occurred more than forty times as frequently as in earlier periods with the diagnosis being offered in office visits in 1994-1995 just 0.01% of the time, but offered 0.44% of the time in 2002-2003 (Moreno, Laje, Blanco, Jiang, Schmidt, & Olfson, 2007). Though the increase was less dramatic for adults, Moreno et al. (2007) reported that adult bipolar diagnoses during mental health office visits increased from 4.77% to 6.58%, a 38% increase. This increase was large enough to generate media coverage (Carey, 2007) and require an explanation.

Alan Frances (2009) a Chairperson of the DSM-IV has attributed the rise in the diagnoses of Bipolar, Autism, and Attention Deficit/Hyperactivity Disorder to an “unintended

consequence" of the manner in which the diagnostic criteria for these disorders were written. He regrets not having insisted upon the inclusion in the DSM-IV of a statement that Bipolar does not occur in children. Francis publicly addressed his colleagues, urging them to write criteria in a manner that would limit false positives in the impending release of the DSM-V. Elsewhere, Frances (2010a, 2010b) has questioned whether "normality is an endangered species" implying that epidemics are created by medicalizing normal human problems, a phenomenon that has been recognized by many others (Horowitz & Wakefield, 2007; Kutchins & Kirk, 1997; Whitaker, 2010).

How the Change in Diagnostics Created an Epidemic

The rise in bipolar diagnoses is probably not attributable to an increase in persons with mania, the principal criterion for Bipolar I disorder. Only a small percentage of individuals will experience manic episodes, estimated to be 0.4% to 1.2% in the DSM-III (1980, p. 217) which is consistent with the estimate provided in the DSM-IV-R (2000, p. 385). Rather the increase in those being called "bipolar" is probably attributable to persons being placed under the larger Bipolar Spectrum tent which includes Bipolar II. In 1994, with the publication of DSM-IV, the diagnosis of Bipolar II was added. Persons with Bipolar II meet criteria for the diagnosis when they have had an episode of Major Depression at some point in their life and have been hypomanic. Episodes of hypomania and mania are similarly defined with two differences: the first being severity and the second that those with mania must display symptoms for one week while those with hypomania meet criteria if they display symptoms for four days. The symptoms of hypomania and mania are the same. The person exhibits irritable or elated mood and exhibits at least four of the following (if irritable mood), or three of the following (with elation): talked rapidly; needed less sleep; reported a rapid increase in ideas; was distracted; displayed inflated

self-esteem; displayed increased goal-directed activity; or spent time engaging in pleasurable, but risky activities. Periods of hypomania do not "cause marked impairment in social or occupational functioning" ; if marked disturbance occurs the diagnosis becomes mania (see DSM-IV-TR, 2000, p. 368).

In the general population, hypomanic episodes are relatively common (Udachina & Mansell, 2007; Wicki & Angst, 1991). Making common behaviors a partial criterion for mental illness would appear to put the psychiatric profession in jeopardy of serious over-diagnosis. The prerequisite for using hypomanic behavior to render a diagnosis of Bipolar II, is the occurrence of an episode of major depression. The Kessler et al. (2005) community studies suggest a general population prevalence for life time occurrence of major depression of 23.2%. Akisal et at. (2000) claim that half of those who have been depressed in their life meet criteria for hypomania and can be more accurately labeled as Bipolar. Consistent with this, in a recent study between 45.7 to 48.3% of those meeting criteria for Major Depression also exhibited "a bipolarity specifier criteria" (Angst et al., 2011). Thus, approximately a 11% of the population would be candidates for a diagnosis of Bipolar II. This new liberal use of common behavior as a criterion for pathology may offer a partial explanation for the increase in Bipolar Spectrum diagnoses.

Viewing the behaviors requisite for a diagnosis of Bipolar II as belonging to the bipolar spectrum was controversial from the outset. When Bipolar II was introduced into the DSM in 1994, some argued that it should be considered a variant of Major Depression (Kupfer, Carpenter, & Frank, 1988). Recent data identifying genes associated with Bipolar I and Bipolar II suggest that common genes are not identified according to Vieta & Suppes (2008). Judd et al. (2003) concur that current genetic evidence suggests that Bipolar I and Bipolar II do not share a

common genetic diathesis. A study by Coryell et al. (1995) tracking persons with Bipolar II and a control group over a ten year period found that those with Bipolar II were no more likely to have a manic episode than controls who never exhibited any hypomanic behavior. Coryell et al. concluded Bipolar II "is probably not simply a variant of bipolar I disorder or of non-bipolar disorder, but is a separate and autonomous disorder (p. 389)." Moreover, Judd et al. (2003) finds that persons with Bipolar I and Bipolar II do not share similar trajectories over time and thus should be considered as separate categories. Thus, the common label for Bipolar I and Bipolar II would appear to be misleading.

Extending the label of Bipolar to those who have met criteria for hypomania has contributed to the perceived legitimacy of the diagnosis of pediatric bipolar. Prior to 1996, there was broad consensus that Bipolar Disorder did not manifest until late adolescence or adulthood (Anthony & Scott, 1960; Goodwin & Jamison, 2007, p. 188; Loranger & Levine, 1978). Then in the1990s, Biederman at Harvard and Geller at Washington University, using broadened criteria for Bipolar that included hypomania, published articles indicating that many children met the formal criteria for Bipolar (see Parens and Johnston, 2010 for historical details). Biederman et al. (1996) did acknowledge the overlap in behavior with ADHD, which had formerly never been linked to Bipolar. Subsequently, Biederman and others published data on the parents of children labeled Pediatric Bipolar. They found that a high percentage of the parents also met criteria for Bipolar (see Littrell & Lyons, 2010a for a review). Unfortunately, the type of Bipolar in the parents was not distinguished during the analysis. By aggregating Bipolar I, Bipolar II, and Bipolar Not Otherwise Specified, the researchers lumped together conditions that are probably not genetically related. But the use of the greatly broadened category enabled them to make the case that the parents were transmitting their heritable disorder to their children. Accepting their

results and conclusions, many physicians began using strong medications, including antipsychotic drugs, to treat children, although not without raising controversy (Parens & Johnston, 2010).

Good Pharmacological Intentions

Concomitant with the rise in bipolar diagnoses among both children and adults has been the increase in the use of newer atypical antipsychotics. While in the period from 1996-1997, 0.8% of the non-institutionalized adult population filled prescriptions for antipsychotics; in 2004-2005, the figure had jumped to 1.3% of the general adult population. The number of children receiving atypical antipsychotics has tripled, jumping from 0.2% to 0.7% of youth in the U.S. population (Domino & Swartz, 2008). In 2007, 1.6% of the children under age 19 covered by 16 state Medicaid programs were receiving antipsychotics; 12.37% of foster children covered by Medicaid programs were receiving antipsychotic medications (Medicaid Medical Directors Learning Network, 2010, p. 14). What can account for the steep increase in prescriptions? The percentage of users of antipsychotics with a diagnosis of schizophrenia has been fairly stable across time periods. The new users of antipsychotics are those with affective disorders (Domino & Swartz, 2008).

The mainstays of treatments for Bipolar I, (lithium, anticonvulsants, atypical antipsychotics) (Goodwin & Jamison, 2007, pp. 728-738) have been extended to treating those with Bipolar II and children with Pediatric Bipolar (Parens & Johnston, 2010).

Pharmacological Downsides

While antipsychotics might very well control mood symptoms in persons with affective diagnosis, there are the adverse health consequences with all antipsychotic drugs, both the older drugs and the newer atypicals. Ho, Andreasen, Ziebell, Pierson, and Magnotta (2011) recently

published the results of their 14 year study in which they used images of the brains of first episode psychotic patients treated with antipsychotic (anti-dopaminergic) drugs over time (average of 7 years). They documented a notable "brain tissue volume decrement" associated with both atypical antipsychotics (quetiapine, risperidone, aripiprazole, olanzapine, clozapine, ziprasidone) and traditional neuroleptics (old drugs such as chlorpromazine). Whereas Ho et al. acknowledged that absence of random assignment precluded their inferring from their study that drugs caused "brain tissue volume decrement", they cited similar findings from animal work. With the macque monkey studies, random assignment to treatment or control in healthy monkeys permitted cause/effect conclusions. After 27 months on doses in the therapeutic range for people, there was a reduction in total weight of brain volume, with the greatest reductions (of from 11.8 to 15.2%) in the parietal lobe. Moreover there was a 14.2% reduction in glial cell (a type of fat cell) numbers (Konopaske et al., 2007; Konopaske et al., 2008). In terms of mechanism through which deficit dopamine signaling might influence brain volume, Miklic, Juric, and Carman-Krzan (2004) discusses the fact that dopamine induces astrocytes (brain glial cells) to release growth factors. These growth factors are vital for the health of the brain (Schwartz & Schechter, 2011; Swartz & Ziv, 2008). In reviewing the data, Ho et al. (2011) acknowledged that a cost/benefit analysis might justify the use of antipsychotics for treating schizophrenia but they questioned the use of antipsychotics in mood disorders.

It should be noted that brain volume decrement is only the latest acknowledged problem associated with antipsychotic medications. The Clinical Antipsychotic Trials of Intervention Effectiveness study found that movement disorders, long known to be associated with traditional antipsychotics, were also found with the newer atypicals, albeit to a lesser extent (Casey, 2006). Moreover, atypicals are associated with weight gain that does not plateau, diabetes, and high fat

levels in blood (a major risk factor for cardiovascular disease) (Goodwin & Jamison, 2007 p. 846) and osteoporosis (Kawai & Rosen, 2010). Andrew Miller (2009) discusses the contribution of compromised dopamine function in depressive symptomotology. If Miller is correct, then drugs which block dopamine function, which the atypcials do, should elevate depressive symptoms.

Unfortunately, the alternative pharmaceuticals to antipsychotics for treatment of Bipolar, which include anticonvulsants and lithium (Goodwin & Jamison, 2007), also have alarming side effects. According to available estimates, lithium will cause end stage renal disease in 16% of the patients over the course of twenty years and lithium induces thyroid gland dysfunction (Bendz, Aurell, & Lanke, 2001; Goodwin & Jamison, 2007, p. 842; Presne et al., 2003). Lithium also causes cognitive impairment (Pachet & Wisniewski, 2003). Both stimulants and antidepressants are purported to accelerate the process of Bipolar Disorder in children (Anand et al., 2000; Fountoulakis, 2008; DelBello et al., 2001). The anticonvulsants carry FDA warnings of suicidal ideation (U.S. FDA, 2008). In 2009, Biederman and colleagues (see Henin et al., 2009) published a study documenting the performance-impairing effects of mood stabilizers, including anticonvulsants, on children with Pediatric Bipolar compared to unmedicated children with bipolar. In short, significant adverse health consequences for all medications used in the treatment of Bipolar Disorder have been recognized.

Alarm over the Medication of Children

Even before the Ho et al.'s (2011) publication of the data on the brain volume decrement associated with antipsychotics, some people did become alarmed at the use of adult medications in children. Allen Frances, the previously cited co-Chairman of the DSM-IV, explaining why he was moved to become a crusader said,"kids getting unneeded antipsychotics that would make

them gain 12 pounds in 12 weeks hit me in the gut. It was uniquely my job and my duty to protect them. If not me to correct it, who? I was stuck without an excuse to convince myself" (see Gary Greenberg, 2010). A study by Crystal, Olfson, Huang, Pincus, and Gerhard (2009) documented the rise of adult medications among privately insured children. The authors noted that the rates were even higher in state Medicaid programs. Raghavan et al. (2005) found that a large number of children in the foster care system were prescribed strong medications. Jeffery Thompson, Washington state director of Medicaid, organized the Medicaid Medical Directors Learning Network (2010) to investigate the rise in the use of strong medications for children. The threats to children have been aired on major television programs. The death of 4 year old Rebecca Riley from a prescription drug overdose was discussed on *60 Minutes* in a segment titled "What killed Rebecca Riley". The Public Broadcasting System aired the Frontline production of *The Medicated Child* and the PBS program Watch List aired *The Medication of Foster Children* (all of which can be watched on line). Presently, the workgroup on mood disorders for children and adolescent tasked with revising the official DSM is considering other diagnoses rather making Pediatric Bipolar official by including it in the DSM-V. However, until the DSM-V is published, clinicians will probably continue to use the diagnosis.

Pediatric Bipolar diagnoses are particularly relevant for children in foster care. It is well documented that children in foster care are far more likely to receive treatment with heavy medications than children in the general population. Moreover, a diagnosis of Pediatric Bipolar is particularly suspect for children in foster care because the symptoms of Bipolar overlap with PTSD and by virtue of having been removed from their families, all children in foster care have experienced trauma (Littrell & Lyons, 2010b). The American Academy of Child and Adolescent

Psychiatry indicates that medicating children with PTSD is not appropriate (Gleason et al., 2007).

The Case for Early Medication

While alarm has been voiced by some, others maintain that treating small children with lithium and the antipsychotics is proper treatment. Chang and colleagues (2010; Chang, Howe, Galleli, & Miklowitz, 2006; Chang & Kowatch, 2007) have resurrected Robert Post's old theory, referred to as the kindling hypothesis, that episodes of extreme moods will change the brain such that mood episodes are more easily triggered. Thus, according to Chang, early treatment might prevent later disorder. Unfortunately, Chang failed to acknowledge the literature which offers little support for the kindling hypothesis (see Goodwin & Jamison, 2007, p. 152). He also failed to acknowledge Ross Baldessarini and colleagues' studies and meta-analysis documenting that early treatment with medications does not change the course of Bipolar I Disorder, that is, early medication does nothing to change the subsequent frequency or severity of mood episodes (Baethge et al., 2003; Baldessarini, Tondo, Baethge, & Bratti, 2007).

Have Outcomes Improved with Medication?

Marcia Angell (2011c), former editor of the *New England Journal of Medicine*, laments the lack of long term outcome studies with a placebo control group in psychiatry. Indeed the Judd et al. (2002) study with its 13 year follow-up, the longest study of persons with Bipolar, did not include a placebo control group. An early naturalistic study with a ten year follow-up by Winokur et al. (1994) concluded that medications were not significantly related to outcome for patients with Bipolar. However, there have been no studies with random assignment to treatment and placebo with long term follow-up. Thus, the question of whether the availability of medications has improved long-term outcomes cannot be addressed directly.

In absence of randomized trials of long term efficacy, outcomes from the pre-drug literature can be contrasted to outcomes in the post drug literature to illuminate the impact of pharmacological treatments. Robert Whitaker (2010), a medical journalist, in *Anatomy of an Epidemic* documents the unfavorable contrast of current outcomes of drug treatments for various psychiatric diagnoses with the outcomes reported in the pre-drug literature. The contrast is particularly stark for Bipolar Disorder. For example, in the pre-drug era, Rennie (1942) found that 93% of patients with mania recovered from their initial episode. Twenty-one percent never relapsed. Of those who did relapse, 30% remained remitted for at least 10 years with an average duration of remission of 20 years. Thus, after an initial period of bipolar symptoms, 51% were remaining well for a significant period of time. A review of early studies prompted Winokur, Clayton, and Reich (1969) to conclude that there "was no basis to consider manic depressive psychosis permanently affected those who suffered from it" (p.21). In contrast, studies of those with Bipolar I in the post drug era find that only 2.1% of persons are asymptomatic during a 12.8 year follow-up; 80% of those who recover relapse within 1.7 years; 23% are continuously unemployed and another 35% are erratically employed (Harrow, Goldberg, Grossman, & Meltzer, 1990; Judd et al., 2002). Examining outcomes for those with Bipolar II, Judd et al. (2003) concluded that Bipolar II is an even more chronic condition than Bipolar I. Zarate, Tohen, Land, and Cavanagh (2000) have also noted the contrast between earlier and current outcomes: "In the era prior to pharmacotherapy, poor outcome in mania was considered a relatively rare occurrence. However, modern outcome studies have found that a majority of bipolar patients evidence high rates of functional impairment" (p. 309).

What Drove the Epidemic?

While changes in the diagnostic criteria enabled the increase in bipolar diagnosis, the pharmaceutical industry probably was the driving force behind some changes in thinking. The most prominent child psychiatrist who promoted the use of bipolar diagnoses for children and the use of off-label medications for those diagnosed with Bipolar Disorder is Joseph Biederman of Harvard University. Biederman is one of a number of leading psychiatrists who have been investigated by Senator Charles Grassley of Iowa who uncovered Biederman's and others' ties to the pharmaceutical industry. Biederman failed to disclose his lucrative ties to drug companies as required by Harvard and the federal agency that sponsored some of his research (Harris & Carey, 2008a; 2008b). Such conflicts of interest in medicine are a growing concern. Marcia Angell (2011a; 2011b) has acknowledged the influence of the pharmaceutical companies to psychiatric diagnoses and treatments.

While raw economic forces can be identified behind some of the revisions in thinking about diagnostic categories, more subtle monetary concerns can also influence the process when diagnoses are provided for individual patients. Private insurance and some state Medicaid systems will only pay for the treatment of those with more severe diagnoses (Danner et al., 2009). With extreme diagnoses, children can receive Supplemental Security Income. Thus, at the individual level, the pressures to render extreme diagnoses are strong.

Time for a Change

It is probably too soon to know whether the documentation of brain volume decrement with antipsychotics will affect prescribing behavior. In the interim, social workers should be developing treatment alternatives to drugs for children who meet criteria for Pediatric Bipolar and for adults meeting criteria for Bipolar II. In the 1970s, prior to the acceleration of pharmaceutical options, B.F. Skinner's point of view prevailed. Rather than assuming that

disruptive behavior is the product of dysregulated biology, identifying environmental factors maintaining troublesome behavior was the recommended strategy. Social work educators should be insuring that students who plan to work with children are trained in observing the child's environment for reinforcing events rather than merely observing the child out of context. In addition to behavior modification, we now have other alternatives as well. Today, approaches to enhance PreFrontal Lobe impulse control functions as described by Vgotsky are capturing attention (Bodrova & Leong, 1996). Dysregulated circadian rhythms have been documented in the etiology of Bipolar disorder (Roybal et al., 2007) and absence of routine increases hypomanic behaviors in most people (Shen, Alloy, Abramson, & Sylvia, 2008). Treatments have been developed for stabilizing circadian rhythms (Frank, Kupfer, & Thase, 2005). If drugs have too many side effects to be relied upon to subdue intrusive behaviors, then social workers need to gear up to offer alternatives. Indeed, Thomas Insel (2009), current 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). Perhaps it is time for a paradigm change.

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