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Review article

More childhood onset bipolar disorder in the United States than Canada or Europe: Implications for treatment and prevention☆

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ABSTRACT

Evidence of a high or increasing incidence of childhood onset bipolar disorder in the United States (US) has been viewed skeptically. Here we review evidence that childhood onsets of bipolar disorder are more common in the US than in Europe, treatment delays are longer, and illness course is more adverse and difficult. Epidemiological data and studies of offspring at high risk also support these findings.

In our cohort of outpatients with bipolar disorder, two of the major vulnerability factors for early onset – genetics and environmental adversity in childhood – were also greater in the US than in Europe. An increased familial loading for multiple psychiatric disorders was apparent in 4 generations of the family members of the patients from the US, and that familial burden was linked to early onset bipolar disorder. Since both early onset and treatment delay are risk factors for a poor outcome in adulthood, new clinical, research, and public health initiatives are needed to begin to address and ameliorate this ongoing and potentially devastating clinical situation.

Contents

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1. Introduction

A higher incidence of childhood onset bipolar disorder in the US has most often been attributed to a variety of factors suggesting that it is artifactual rather than real. These factors have included: a broadening of the diagnosis, diagnostic differences between countries, over diagnosis, and artificial coding related to reimbursement. This skeptical view of the data has resulted in neglect of the magnitude of the problem in terms of clinical therapeutics, public health practices, and a treatment research agenda.

In this manuscript we review the evidence that much of the high incidence is very likely real and deserving of greater and multifaceted attention. The evidence reviewed includes: comparative studies of US versus European populations of patients with bipolar disorder, epidemiological studies, clinical samples, prospective follow up studies of children with a bipolar diagnosis, and studies of high risk offspring of a parent with bipolar disorder that were carried out in the US compared to non-US sites. In addition, potential reasons for the higher incidence in the US than in Europe are explored and include evidence of greater genetic vulnerability; more childhood adversity mediating psychosocial stress vulnerability; and other potential factors such as diet and higher rates of obesity with associated inflammation. Other possible contributors to the increased presence of childhood onset bipolar disorder include cohort (year of birth) and anticipation (generational) effects.

Assuming that this accumulation of evidence supports the view that many aspects of bipolar disorder present a greater problem in the US than in many other countries, several suggestions for better addressing this situation are offered. These are important to consider as more than a dozen studies (as cited below) suggest that childhood onset bipolar disorder runs a more difficult course and has a poorer outcome than adult onset illness. Multiple approaches are likely to be necessary to address the magnitude of the problem and its long-term consequences. A very extensive revision of the current treatment and research agenda will likely be necessary to begin to reverse some of the multigenerational trends for greater illness adversity in the US compared to Europe.

2. Types of studies and data

2.1. Comparative studies involving patients inside and outside of the US

Four studies directly compared patients from the US to those in Europe or Argentina.

1. In the Stanley Foundation Treatment Outcome Network (SFBN) more than 900 outpatients were recruited and followed prospectively with cross sectional and daily life chart ratings from 1995 to 2002. About 75% were bipolar I and 25% bipolar II based on SCID diagnoses (Post et al., 2014a). They came from four sites in the US (Los Angeles, Dallas, Cincinnati, and Bethesda), and from three sites in Europe (Utrecht, the Netherlands, and Freiberg and Munich, Germany; abbreviated here as Europe). In the US versus Europe, we found onsets in childhood (before age 13) in 31.1% vs 5.6%; in adolescence (13–18) 38.1% vs. 26.6%; in young adulthood (19–29) 19.8% vs 42.2%; and in older adulthood (30 and greater) 11.0% vs 23.7%. Thus, some two thirds (69.2%) of the onsets in US adult patients with bipolar disorder started in childhood or adolescence, and only one third (32.2%) in Europe. Regarding concerns that our US sample might be non-representative, the percentage of early onset was virtually identical to that seen in the STEP-BD cohort (Perlis et al., 2004) where recruitment was from entirely different cities and academic institutions in the US than those in the SFBN (now referred to as the Bipolar Collaborative Network or BCN)
2. Bellivier et al. (2014) compared patients with bipolar disorder in the Pittsburgh case registry in the US to those from 10 different European countries. Using an admixture analysis they found a distinct increase in the youngest onset patients in the US (63%) compared to 25% in Europe, such that the average age of onset difference in this subgroup was 4.5 years.
3. Etain et al. (2012), using the same admixture analysis to define an early onset subgroup, also found that 68% of the bipolar patients in the US (from the Bipolar Phenome Database) belonged to this group in contrast to only 42% of the patients from France who were in this early onset subgroup.
4. Holtzman et al. (2015a) found a much earlier mean age of onset of bipolar disorder in the US (17.9 ± 8.4 yrs.) compared to that in Argentina (27.1 ± 11.4 years).

2.2. High risk offspring studies conducted in the US versus elsewhere

A substantial series of studies have examined the incidence and age of onset of bipolar disorder in the offspring of parents with bipolar disorder. Compared to those conducted elsewhere, those conducted in the US have seen more early onset bipolar disorder in the offspring followed prospectively. Exact comparisons across studies are not possible because of differences in the age range of the offspring studied and duration of follow up. However, those in the US report a percent incidence of bipolar disorder in the range of 3% to 16% (Birmaher et al., 2009b; Chang et al., 2000; Henin et al., 2005; Nurnberger et al., 2011; Singh et al., 2007; Zappitelli et al., 2011). In contrast, Duffy et al. (2007) from Canada, Wals et al. (2004) and Hillegers et al. (2005) from the Netherlands, Vandeleur et al. (2012) from Switzerland, and Grigoroiu-Serbanescu et al. (1989) from Romania, rarely saw bipolar onsets prior to late adolescence or early adulthood. They tend to see a temporal evolution of onsets first of anxiety disorders in the youngest children, followed by depressions, and only later bipolar disorder (Duffy et al., 2007, 2009; Hillegers et al., 2005)

Birmaher et al. (2010), while not making direct comparisons with European offspring studies, reported that the US parents with bipolar disorder had a substantial incidence of many other psychi-