

How does a Developmental Perspective inform us about the early Natural History of Bipolar Disorder?

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Abstract

Objective: The focus of this paper is to explore how a developmental perspective can advance understanding of the clinical trajectory into bipolar disorder (BD) and clarify controversies regarding the diagnosis in youth. **Method:** In this selective review, we focus on findings from longitudinal studies of general population and high-risk pediatric cohorts in order to inform our understanding of the development of BD in youth. Also highlighted are related aspects of the debate about the diagnosis in young children and a discussion of the implications of the findings for advancing early detection and intervention clinical and research efforts. **Results:** Evidence overwhelmingly suggests that BD typically onsets in adolescence and early adulthood, with the depressive polarity of the illness dominating the early course. Non-specific childhood antecedents have been noted in some high-risk individuals. However, in youth *without* a confirmed familial risk of BD, manic-like symptoms have little prognostic significance for BD and not uncommonly form part of the normative adolescent experience. Over-emphasis of symptoms and reliance on parent report alone, alongside the relative neglect of the child's developmental stage and risk profile, contributes to the over diagnosis in young children and under recognition of BD early in the clinical course. **Conclusions:** Longitudinal population and high-risk studies over development have made major contributions to our understanding of the early natural history of BD in youth. Implications call for a different diagnostic approach to facilitate accurate identification of youth in the early clinical stages of psychiatric disorders and to differentiate between the emerging illness trajectories and transient normative symptoms in childhood and adolescence.

Key Words: bipolar disorder, children and adolescents, longitudinal, developmental, diagnosis, clinical course, psychopathology

Résumé

Objectif: Cet article vise à explorer comment une perspective développementale peut faire mieux comprendre la trajectoire clinique du trouble bipolaire (TB) et clarifier les controverses à propos du diagnostic chez les adolescents. **Méthode:** Dans cette recherche sélective, nous nous penchons sur les résultats des études longitudinales dans la population générale et sur les cohortes pédiatriques à risque élevé afin d'éclairer notre compréhension du développement du TB chez les adolescents. Nous présentons aussi les aspects liés au débat à propos du diagnostic chez les jeunes enfants, ainsi qu'une discussion des implications des résultats pour l'avancement des initiatives de recherche, et de détection et d'intervention cliniques. **Résultats:** Les données probantes suggèrent massivement que le TB débute habituellement à l'adolescence et au début de l'âge adulte, et que la polarité dépressive de la maladie domine le cours au début. Des antécédents dans l'enfance non spécifiques ont été observés chez des personnes à risque élevé. Cependant, chez les adolescents *sans* risque de TB familial confirmé, les symptômes semblables à la manie ont peu de signification pronostique pour le TB, et il n'est pas rare qu'ils fassent partie de l'expérience normative de l'adolescence. La surestimation des symptômes et le fait de se fier uniquement aux déclarations des parents, de concert avec la négligence relative du stade développemental de l'enfant et de son profil de risque contribuent au sur-diagnostic chez les jeunes enfants et à la sous-identification du TB dans les débuts du cours clinique. **Conclusions:** Les études longitudinales de la population et du risque élevé au cours du développement ont fortement contribué à notre compréhension des débuts du cours naturel du TB chez les adolescents.

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Les implications demandent une approche diagnostique différente pour faciliter l'identification exacte des adolescents aux premiers stades cliniques de troubles psychiatriques, et pour différencier entre les trajectoires naissantes d'une maladie et les symptômes transitoires normatifs de l'enfance et de l'adolescence.

Mots clés: trouble bipolaire, enfants et adolescents, longitudinal, développemental, diagnostic, cours clinique, psychopathologie

Introduction

In this paper, we focus on the importance of a developmental perspective to inform the early detection of evolving bipolar disorder (BD) in youth, drawing on findings from longitudinal epidemiological and familial high-risk studies. We also discuss the implications of these observations for the advancement of early accurate diagnosis and intervention in vulnerable pediatric populations and address some diagnostic assessment complications unique to children.

The developmental perspective and diagnosis

Debate on the validity of the diagnosis of mania in young children spans more than half a century (Carlson & Glovinsky, 2009), fuelled by whether one views BD more conservatively, requiring clear episodes that mark a distinct change from premorbid levels of function (Leibenluft, 2011), or more liberally including: 1) medication-induced activation symptoms that some consider to be mania-induction (<http://www.psychiatrytimes.com/display/article/10168/52296>); and, 2) subsyndromal mood symptoms conditions largely in those at familial risk; a debate not unique to child psychiatry (Strakowski, Fleck, & Maj, 2011). In addition, however, in child psychiatry, the liberal viewpoint conceptualizes childhood mania as: 3) severe irritability and explosive outbursts (Mick, Spencer, Wozniak, & Biederman, 2005) in the relative absence of discrete episodes. The liberal viewpoint also includes: 4) the modification of the definition of manic symptoms, (Geller et al., 2002), a modification with which not everyone agrees (Harrington & Myatt, 2003).

Other developmentally related complications include how development changes the way in which we gather information, how criterion symptoms and behavioral definitions change with age, and which age related comorbid conditions complicate the differential diagnosis of mania. A further consideration is whether symptoms that occur in the general population have the same implications in a high-risk population and whether that, too, is contingent upon age.

Identifying clinical illness episodes in youth is an issue which requires a developmental approach. While there is probably agreement that younger children need parents to provide information about symptoms and behaviors, adolescents are felt to be sufficiently insightful about their internal and external state that in most studies they are either

the first informant (Kaufman et al., 1997) or the only informant (Lewinsohn, Seeley, Buckley, & Klein, 2002; Kessler et al., 2012). Inter-rater agreement for most symptoms in child and adolescent psychiatry is fairly modest with correlations between 0.2 and 0.3 (see (De Los Reyes & Kazdin, 2005) for review). However, in a recent community study in the United Kingdom, agreement between the parent and child (age ten through adolescence) for manic symptoms was 0.02 (Stringaris, Stahl, Santosh, & Goodman, 2011)! Furthermore, in those few studies where information was also obtained from teachers, parents have not infrequently reported serious symptoms of mania, while teachers have reported absolutely no symptoms (Arnold et al., 2012; Carlson & Blader, 2011). It is difficult to conceptualize clinically significant manic episodes that last for months, but no one other than the parents observe. Nevertheless, this aspect of data gathering (using only one informant) has been built into the diagnostic approach to BD in youth, and differs from the approach in adults.

How easily can euphoria and grandiosity, two of the important symptoms of mania, be extrapolated downward to children and are the diagnostic implications the same? The concept of euphoria (e.g. "intense feelings of well-being, elation, happiness, ecstasy, excitement, and joy; an intense state of transcendent happiness combined with an overwhelming sense of contentment") is quite sophisticated, and it is not always clear how well a younger child might understand it - especially a child with comorbid attention deficit disorder (ADHD), learning and/or language disorders. In studies that have separated parent and child responses, it is the parent's response that has been coded, as the child endorses the symptom less frequently (Tillman et al., 2004). Our experience has been that when a parent describes the child as euphoric, as evidenced by silly and giddy behavior, the child provides a reasonable, developmentally appropriate explanation (Carlson & Meyer, 2006). Under the circumstances, it is necessary to interview the parent and child together to clarify that they are identifying the same situations and to assess, based on all information, the clinical meaning of the symptoms, if any.

Grandiosity is another important manic symptom that may be influenced by a child's developmental age and comorbid condition. For instance, boys with ADHD often have an unrealistically positive view of their popularity and ability (Owens, Goldfine, Evangelista, Hoza, & Kaiser, 2007), which is perhaps evidence of poor judgment and difficulty reading social cues rather than true grandiosity. This

tendency is also seen in aggressive and learning disabled children. Given the frequency with which ADHD, learning and aggressive problems are seen in samples of putatively manic children, a question arises as to the diagnostic meaning of a child's bragging or lack of insight into the reality of his social and academic failure. Children on the autism spectrum and other children with language comprehension problems are also likely to struggle with the abstract nature of questions addressing self-awareness, and for that matter, mood state (Carlson & Meyer, 2006). These factors are important to consider before concluding that such children have mania-driven grandiosity.

Prospective developmental studies

Following on the fact that our diagnostic approaches emphasize symptoms without taking into account the context or developmental stage of the individual patient, in order to advance early detection and effective intervention, it is vital that we have a good understanding of the early natural history of major psychiatric disorders such as BD. By longitudinally mapping illness trajectories we will be able to identify at which point these differ from each other and from transient normative symptoms in youth. Furthermore, important predictive factors such as family history and place along the developmental trajectory can inform the clinical meaning of any current symptoms in individual patients.

Longitudinal epidemiological studies

There have been several large community based prospective longitudinal studies that can inform us about the early natural history of BD. One such study, the Oregon Adolescent Depression Project, reported on psychopathological outcomes in a randomly selected sample of 1709 high school students with a mean age 16.6 years (Lewinsohn, Klein, & Seeley, 2000). Teens were prospectively reassessed at one-year post baseline (T2) and a subset at age 24 years (T3). Full-threshold mania was observed in two cases. The remaining 16 cases were considered relatively mild (i.e. mostly BD II and cyclothymia; no hospitalizations). The peak hazard of onset of BD was in mid-adolescence, with just under 50% showing non-recurrence in adulthood. Sub-threshold manic symptoms occurred in over 5% of the population, peaking in adolescence and discontinuous with BD in adulthood (Lewinsohn, Seeley, & Klein, 2003). In a recent report on this cohort, sub-threshold BD predicted full-threshold depressive and anxiety disorders in adulthood, while sub-threshold conduct disturbance and full-threshold depressive and substance use disorders predicted BD (Shankman et al., 2009).

The Dunedin Multidisciplinary Health and Development Study reported on a birth cohort of 1037 children who completed baseline comprehensive assessments at age three and were followed up to age 26 years (Kim-Cohen et al., 2003). A main finding of this study was that the majority of adults with full-blown psychiatric disorders met diagnostic criteria

for psychiatric disorders already in adolescence. This study also demonstrated that the nature of the antecedent juvenile diagnoses could be consistent with the adult illness, but could also be different (heterotypic) in nature. Specifically in regard to adult mania (at age 26 years), 93% of subjects had a prior diagnosis in childhood or adolescence, including conduct, oppositional disorder or juvenile depression, but not pediatric mania. In contrast to adults diagnosed with schizophreniform disorders, adults with BD had normal developmental histories with no evidence of impairment in neuromotor, receptive language or cognitive deficits (Cannon et al., 2002).

The Early Developmental Stages of Psychopathology study is another prospective investigation of the development of psychiatric disorders in a representative sample of over 3000 adolescents and young adults (aged 14-24 years at baseline) living in and around Munich (Tijssen et al., 2010b). This study reported that hypomanic symptoms in the general adolescent population are common, transitory and typically not predictive of subsequent psychopathology or mental health care use (Tijssen et al., 2010c; Tijssen et al., 2010a). Specifically 25% of adolescents experienced hypomanic symptoms at one assessment time over a three-year period, while only 2.6% experienced hypomanic symptoms over two time periods. Further, persistence in symptoms showed a dose-response relationship with the risk of developing a hypomanic episode.

Using a different approach to address developmental differences in mania, Cicero and colleagues (Cicero, Epler, & Sher, 2009) examined data from the National Comorbidity Survey Replication (Kessler & Merikangas, 2004) ($N = 9,278$) and the National Epidemiological Survey of Alcohol and Related Conditions ($N = 43,093$ and follow-up, $N = 34,653$). They found that among 18-24-year-olds, rates of 12-month bipolar spectrum disorder were 5.5%-6.2% (Grant et al., 2005). In the rest of that decade, rates dropped (to 3.1%-3.4% among 25-29 year-olds). In fact, rates continued to drop over subsequent decades. This raises the question as to why, if pediatric BD is a chronic illness, the rates are not level or even increasing with each successive decade? The authors considered that some ascertainment bias due to early mortality, institutionalization, incarceration, and homelessness might explain some of this drop, but not completely. As reported in the aforementioned studies, the young sample was significantly impaired, but it remains to be seen whether their impairment was due to their manic symptoms, depressive symptoms or to the multiple comorbidities identified in parallel. Like the Tijssen data (Tijssen et al., 2010c), these findings suggest that what is elicited in standardized interviews directed at identifying manic symptoms is not necessarily the same thing as clinical BD.

In summary, findings from prospective longitudinal studies of general population cohorts over childhood and adolescence suggest that hypomanic symptoms in of themselves

may be part of the normative adolescent developmental experience and not predictive of BD, or for that matter of any psychiatric outcome. However, persistent symptoms, especially in association with comorbidity or distress, may identify a fraction of this population at risk for subsequent psychopathology, both mood and non-mood related. Furthermore, findings from these studies support that non-specific or non-mood childhood psychiatric disturbances can antecede the subsequent onset of BD.

Longitudinal high-risk studies

Major psychiatric disorders such as schizophrenia and BD run in families and based on twin and adoption studies, the familial clustering has a strong genetic basis (Hamshere et al., 2011). In fact, the most robust risk factor for developing BD is a confirmed family history as evidenced recently in a large population study (n=2.7 million) showing the risk of BD up to age 52 jumping from 0.48% in individuals with neither parent affected, to 4.4% in those with one parent affected and up to 25% in those with both parents affected (Gottesman, Laursen, Bertelsen, & Mortensen, 2010).

Over the past 30 years, there have been several longitudinal prospective studies reporting on the clinical outcomes among offspring of BD parents followed over development. These high-risk studies have substantially informed our understanding of the natural history of this illness in vulnerable youth (see Duffy, 2010 for review). While cross-sectional studies have reported that child and adolescent offspring of BD parents manifest an unexpectedly broad range of lifetime disorders, longitudinal studies have demonstrated an evolutionary shift in psychopathology within high-risk individuals from non-specific disorders in childhood to depressive disorders in early adolescence and finally BD spectrum disorders in later adolescence and early adulthood (Duffy, Alda, Hajek, Sherry, & Grof, 2010).

To wit, in a longitudinally studied offspring cohort from the Netherlands (Hillegers et al., 2005), BD typically debuted as a depressive disorder in mid-adolescence and was followed on average 4.9 (3.3 SD) years later by the first activated episode. In this study, internalizing symptoms and subjective problems, including attention in adolescent girls, preceded the onset of frank mood disorders. However, there was no evidence of full-blown ADHD or conduct disorders predicting mood psychopathology. It should be noted that in this cohort, the high-risk families were largely intact and comparable in terms of socioeconomic status to the Dutch general population, suggesting a relatively reduced burden of general psychopathology in the families, compared to more heterogeneous and bilinear samples in other high-risk studies (see Duffy et al., 2011 for review).

Similar findings have been reported in a longitudinal study of well-characterized families from the Amish community in the United States (Shaw, Egeland, Endicott, Allen, & Hostetter, 2005). In this population, there is extensive

community support, typically only one parent ill per family, and high quality of nutrition, social rhythm and family cohesion. Against this backdrop, children flagged as “at risk” for developing clinically significant psychopathology manifest anxiety and depressive symptoms early in childhood, which shifted to include more activated symptoms later in development. Interestingly, these mixed symptom clusters were described as episodic rather than chronic in nature. Further, full-blown hypomania or mania was not seen during early childhood, while ADHD and other childhood behavioural disorders were also relatively absent.

In a Canadian longitudinal study reporting on the offspring of parents with either a lithium-responsive (LiR) or a lithium non-responsive (LiNR) form of BD (other parent well), an elevated rate of childhood sleep and anxiety disorders in both offspring subgroups was reported, as well as an increased rate of neurodevelopmental presentations (ADHD, learning disabilities, cluster A traits) among the offspring of LiNR parents (Duffy, Alda, Crawford, Milin, & Grof, 2007). Furthermore, a recent updated analysis revealed a 2.5 fold increased risk of major mood disorders (major depression, BD) in those offspring with, compared to those without, an antecedent childhood anxiety disorder (Duffy et al., 2010). An exploratory analysis revealed that antecedent anxiety in the offspring was not associated with an increased risk of anxiety disorders in adult family members. These findings suggest that anxiety disorders (and perhaps other non-specific childhood antecedents) in children at confirmed genetic risk of BD are related to and predict the development of BD. On the basis of these observations, Duffy and colleagues proposed a clinical staging model describing the early clinical trajectory in the development of BD in high-risk children and adolescents (Duffy et al., 2010; Duffy, Alda, Hajek, & Grof, 2009).

In summary, consistent with findings from prospective epidemiological studies, longitudinal studies of children and adolescents at *confirmed* familial risk of developing BD have clarified that the illness typically starts with depressive episodes and the depressive polarity of the illness dominates the clinical picture in adolescence. Further, that in some high-risk offspring, antecedent childhood disorders can be non-specific and include anxiety and sleep disorders. In families at risk for typical lithium responsive BD, these manifestations tend to be episodic rather than chronic. Furthermore, in those children at genetic risk of developing psychotic spectrum BD (offspring of LiNRs), neurodevelopmental disorders may be among the childhood antecedents. The latter observation reflects overlap both clinically and neurobiologically with findings reported in children at familial risk of developing schizophrenia (Murray et al., 2004).

The developmental perspective and the future

Evidence from longitudinal prospective studies support that, adult psychiatric illnesses often originate from, not only similar (homotypic), but seemingly different (heterotypic), sub-threshold symptoms and syndromes in childhood (Rutter, Kim-Cohen, & Maughan, 2006). Further, within identified high-risk cohorts, psychiatric illnesses such as BD have been shown to evolve through a series of phenotypically different clinical stages (Duffy, 2010). These latter observations are consistent with either: (i) an underlying shared vulnerability that in interaction with other influences during sensitive developmental periods results in different disorders; or, (ii) that the same underlying disease manifests differently over development and the early course, perhaps related to the developmental stage of the central nervous system (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). In addition, complications of the primary illness, as well as the burden of illness and treatment effects influence the clinical and neurobiological manifestations of illness; which interact with the manifestations of the primary illness over development and course.

Therefore, it is our view that the focus of our diagnostic systems on symptoms in isolation of the developmental context of the patient is inadequate for the accurate early detection of major psychiatric disorders in youth and limits the opportunity for effective early intervention. This is especially true when one considers that adolescents are transitioning through a period of accelerated neurobiological and psychosocial development, suggesting that effective intervention during this time might have multiplicative and enduring benefits. In order to understand the origins of major psychiatric disorders in youth and to identify targets for effective and safe early treatment, we advocate the need to shift to a developmental approach to diagnosis that takes psychosocial and biological (genetic factors, pubertal stage) context and the natural history of psychopathology into account.

The debate around the diagnosis of mania in children, in conjunction with findings from the longitudinal epidemiological and high-risk studies that have followed, have provided a firm basis of evidence emphasizing that our current approach to diagnosis is severely limited and requires a major rethink. This diagnostic system, as pointed out by Grof (Grof, 2010), was based on observations of end-stage illness in adults admitted to asylums over 100 years ago. As illustrated by Carlson and others (Carlson, 2011), the diagnostic approach has been further influenced by researchers adopting standardized ratings of symptoms without reference to developmental stage or risk of the individual.

If we are to advance early detection of major psychiatric illnesses in youth and identify novel targets for early treatment intervention, then we need to incorporate the evidence starting with a carefully confirmed family history (i.e. what

is this child at risk for?) and a good knowledge of the early natural history and developmental trajectories of major psychiatric illness in youth (i.e. what do the major psychiatric illnesses look like early in the course and development?). The conundrum of diagnosis is most evident in, but not isolated to, Psychiatry. That is, with the technological advances in diagnostic medicine, there is concern that practitioners have been trained to interpret test results without properly considering the clinical profile of the patient; including a careful history of the presenting illness, a detailed family history of illness and the developmental stage of the individual patient. The difference in Psychiatry, unlike many other medical diseases is that we lack a good understanding of the early natural history, associated pathophysiology and proven effective early interventions.

An obvious contradiction to the evidence discussed here is reflected in the reality that child and adult psychiatry remain largely separate medical and academic domains, housed in distinct institutions, precluding continuity of clinical care and research. This situation has contributed to the tragic paradox that youth aged 15-24 years of age are the least well served population in Canada in terms of their mental health needs, and yet the highest risk group for the onset of major psychiatric disorders (Waddell, McEwan, Peters, Hua, & Garland, 2007). Given that adolescence is also the critical defining period for academic, vocational, psychological and interpersonal development, this failing should be viewed as a national crisis and a major health priority.

Concluding remarks

Controversy has fuelled constructive longitudinal research yielding practical and important clinical implications. Now we need to revise our methods of diagnosis in youth and service organization accordingly. Specifically, we need to take a developmentally sensitive approach to diagnosis and provide provision for assessment of children of psychiatrically ill parents in a seamless integrated manner. We also need to establish longitudinal high-risk surveillance and early intervention programs for children of parents with serious psychiatric disorders, as they are the most at-risk and easily identifiable group of vulnerable youth.

Much important work remains in order to understand the pathophysiology of evolving psychiatric illness in youth and to identify important early intervention opportunities and protective influences. We believe that Psychiatry, especially Youth Psychiatry, is entering a new and optimistic era, fuelled by a leap in our understanding of the early natural history major psychiatric disorders and important early developmental influences. If we stay the course, we should be in a much better position to make a real difference to the outcomes of vulnerable youth in our own lifetime as practicing clinicians.

Acknowledgments / Conflicts of Interest

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