Childhood bipolar disorder: diagnostic and treatment challenges

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Abstract

Since the peak onset of bipolar disorder occurs in late adolescence, there is great interest in identifying and treating this disorder early in young people. However, the diagnosis of bipolar disorder in children and adolescence can be challenging and this paper outlines some of these diagnostic difficulties. Treatment is similarly challenging, since the evidence base in this age group remains limited and medication can be associated with significant adverse effects. The available treatment options are discussed, together with the role of the GP in recognising and managing this condition.

Key words: bipolar, mania, depression, child, adolescent, diagnosis, treatment

Introduction

There has been much publicity in recent years regarding an 'epidemic' of childhood bipolar disorder (BPD). In the US, clinical studies have reported a sharp increase in prevalence, with a 40-fold increase in clinic visits over recent years (1). However, there is no evidence from international epidemiological studies to suggest that the true rate is increasing in the community (2). This indicates that there is a marked discrepancy between recognition by clinicians and diagnoses made by researchers, and this has been the subject of much controversy.

BPD is generally considered to be an uncommon condition in children that becomes more frequent in the teenage years (2, 3), with the peak onset of the disorder occurring in late adolescence (4). Since many adults with BPD also report early symptoms in childhood (5), there has been much interest in the recognition of bipolar disorder in children and adolescents, in the hope that early diagnosis and treatment might improve longer-term outcomes.

BPD is associated with significant levels of morbidity and a high risk of both suicide and suicide attempts, particularly in young people (6). Children and adolescents with BPD have greater levels of severity and complications than adult-onset cases (7); the course of the illness is more protracted, making these younger-onset bipolar cases appear more like treatment-refractory adult-onset cases (8). For example, in the COBY study, adolescents continued to have symptoms for 60% of the time during a four-year period and, in comparison to adult cases, were more likely to have repeated changes in polarity and a mixed presentation (9, 10). Only 20% experienced complete recovery after admission, with most continuing to suffer from a significant degree of impairment (11). Despite the evidence regarding the severity of this condition, diagnostic delay is greater in these early-onset cases (5). The COBY study reported that the length of time to diagnosis was around 10yrs, and for each year of illness, there was a corresponding 10% less chance of recovery (12).
Although there is clearly a need to recognise this disorder in young people, early diagnosis is challenging and there are concerns about both inappropriate over-diagnosis and under-diagnosis of BPD. This paper will outline some of the developmental challenges in early diagnosis, together with some of the diagnostic controversies. The paper will also outline treatment strategies, the risks and

benefits of medication, and the role of the GP in management.

Diagnostic Challenges

Developmental context

a) Distinguishing normal behaviour

Some of the key features of BPD may be seen commonly in children and adolescents, and need to be distinguished from normal behaviour. For example, mood swings are common and need to be considered in a developmental context when assessing for BPD. Brief periods of elation and excitability are normal in response to positive life events; in order to diagnose (hypo)mania, the episode will need to be prolonged with a clear onset and offset, and be accompanied by other symptoms of mania. Functioning also needs to be impaired but, in cases of mild hypomania, functioning may temporarily improve with a greater sense of wellbeing, increased confidence and productive activity; recurrent symptoms are, however, associated with numerous difficulties.
Grandiosity is an example of another symptom which needs to be considered within a developmental context. Younger children may make grandiose statements which are in keeping with their developmental age and would not necessarily indicate a symptom of mania. Children may state that they are the best in the world at sport, that they are the strongest, the fastest and brightest, or may believe that their behaviour may be beyond consequences ('I'll fight the police so they can't get me'); these types of statements may not be unusual for their developmental age.

b) Comorbidity

Comorbidity is common, complicating both diagnosis and treatment; it is associated with poorer outcomes (13). In younger children, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), speech and language disorders and autistic spectrum disorders (ASDs) with accompanying mood lability can make diagnosis difficult. ADHD and behaviour disorders are frequently comorbid with mania in children (14, 15). In adolescents, diagnosis can be complicated by comorbid substance abuse and emerging personality disorder (16, 17). Greater comorbidity also increases the risk of self-harm and attempted suicide (6).
Even in the presence of a history of any of these disorders, there needs to be evidence that there has been a marked change of usual behaviour for that child in order to make the additional diagnosis of a (hypo)manic episode.

c) Symptom overlap

Diagnosis is also made difficult by the degree of symptom overlap with a number of disorders, particularly with regard to irritability. For example, ADHD symptoms in children can resemble mania, since these children can talk excessively, are overactive and impulsive, can be giddy and irritable, and often have little need for sleep. ODD children can also behave in an impulsive, irritable and grandiose manner. However, the key factor which separates these behaviours from (hypo)mania, is the presence of a change in behaviour or personality in (hypo)mania; ADHD and ODD symptoms are chronic, but manic episodes have clear onsets and offsets.

Diagnostic criteria

Opinions differ on the developmental appropriateness of applying adult criteria. Classical mania meeting DSM-IV-TR criteria (acute and clear onset and offset of symptoms, lasting at least 1 week for mania) appears to be rare in young people (18, 19). Mania in adolescents is often complicated, with rapid cycling and mixed manic/depressive features (20). Atypical presentations are controversial in terms of their true relationship to BPD, and also in terms of diagnostic agreement (21). Varying diagnostic approaches have been proposed, but the implications of these approaches for treatment and prognosis remain unclear (22). The key issues under investigation are whether brief periods of hypomania (less than 4 days) are a subtype of bipolar disorder and whether irritability should be a

core symptom.

Duration

US researchers have described ultrarapid cycling in children (brief, frequent manic symptoms lasting hours to days, but less than the 4-day prerequisite for hypomania) and 'ultradian cycling': repeated brief (minutes to hours) daily cycles (23). The concept of 'ultradian' cycling is controversial and may be confused with brief periods of mood lability which are environmentally driven or brief mood variations within an episode (9). For example, during an episode of depression, a child's mood can fluctuate from sad to irritable and even cheerful, if distracted.

Although the concept of ultradian cycling is controversial, there is evidence, however, that episodes of less than the prerequisite 4 days for hypomania may be of significance. Data in young people with only a 2-3 day symptom duration have shown that the outcomes for these individuals are similar to those with a 4-day duration of symptoms (24). Research suggests that about half of these cases will progress to bipolar I/II over 5 years and that they have similar levels and types of difficulties (24, 25). The diagnosis of bipolar disorder not otherwise specified (NOS) is used for cases that do not meet the current minimum duration criteria, however bipolar disorder-NOS is not well-defined. In order to avoid over-diagnosis, researchers have suggested that a minimum number of days, symptoms and episodes, together with impairment, should be present to diagnose bipolar disorder-NOS (24, 25).

Irritability

Irritability is a symptom that is a core feature not only of BPD but also of a number of childhood disorders, including both the emotional and behavioural disorders (26). The UK NICE guidelines view on irritability is that it should not be used as a core criterion in BPD, except in older adolescents, since it is such a non-specific symptom (27). Very few young people with BPD will present with irritability without elation but they do appear similar to those with elation (28); in these cases mania should only be diagnosed if accompanied by other manic symptoms and there are clear episodes.

One line of investigation has been whether chronic irritability in young children might be a precursor of future rapid-cycling adult BPD. A condition called severe mood dysregulation (SMD) has been studied, which describes children with chronic irritability, hyperarousal and ADHD. Although SMD has been shown to be associated with significant difficulties, it does not appear to increase the risk for future bipolar disorder (29). Temper dysregulation disorder with dysphoria (TDDD) is a new category, based on SMD, that has been proposed for inclusion in DSM-V. This category has been devised for children with chronic irritability and temper outbursts who do not meet criteria for BPD in order to avoid the problem of over-diagnosis of bipolar disorder in young people in the US. However, numerous concerns exist regarding this proposal. In particular, this category may pathologise many children unnecessarily and create new additional problems with inappropriate over-diagnosis of TDDD (30).

The problem of under-recognition or over-recognition

There is a wide variability in reported rates of BPD between international clinical samples. For example, high clinic rates of mania (16%) have been reported in specialist US ADHD centres (31), in contrast to UK clinical data where prepubertal mania appears to be very rare (32). In a survey of 200 UK children and adolescents with ADHD only one case of bipolar disorder-NOS was reported (33). Since epidemiological studies indicate that the rates of bipolar-I are similar internationally (2), there is no evidence to suggest that there is a true epidemic of BPD and differences between clinical studies are likely to be a result of cultural influences as well as differing approaches to diagnostic ascertainment in young people. A recent meta-analysis of community diagnostic studies found that the greatest variability in rates between the US and other countries was for subsyndromal BPD. Hence these differences may be partly attributed to the lack of clarity regarding the diagnosis of bipolar disorder-NOS where it is recognised more frequently in the US, and potentially overlooked elsewhere (2). An

additional factor is that there is also ambiguity around the interpretation of mania symptoms in DSM-IV-TR (34), resulting in variation in diagnostic instruments based on this (35).
A study of UK and US clinicians investigated views on diagnosis in a range of case vignettes (21). Although there was agreement regarding a classical presentation of BPD, there was less agreement for more complex cases, with US clinicians being more likely to diagnose mania. There appear to be differing interpretations of symptom presentations by clinicians. It is possible that the recent high level of media exposure regarding BPD in the US, together with differences in health organisation and delivery may be contributory factors to these findings. In contrast, the UK NICE guidelines advocate a conservative view to diagnosis in children and adolescents, whereby the adult criteria for a manic episode need to be met, and with less emphasis on irritability; NICE also states that bipolar-II should not be diagnosed in children and younger adolescents, in view of the uncertainties regarding the diagnostic criteria. It is likely that this more conservative view on diagnosis has also contributed to the differing cross-national perspectives on this condition.

The issue of over-diagnosis and underdiagnosis is vitally important, as it has significant implications for the child. Over-diagnosis brings a potentially stigmatising diagnostic label with possible life-long implications and potentially inappropriate treatment that could have serious adverse effects; the danger of under-diagnosis is that a serious mental illness may be missed and not treated appropriately, with significant risks of suicidality and impaired quality of life. Therefore the issue of diagnosis remains an important area for research, in order to improve agreement on diagnostic criteria and aid the reliability of clinical detection.

The search for a prodrome

We do not yet have reliable markers confidently to identify those cases at high risk of converting to BPD (36). Young people with a family history and recurrent depression (37) are at a higher risk but studies of prodromal features have not identified symptoms that are specific to BPD (36, 38, 39). In those cases with a familial risk, the conversion rate to BPD is still relatively low. For example, a 10 year follow-up study of Amish offspring of bipolar parents did not identify any cases of BPD in late adolescence (40).

Although more specific markers are not yet available, there is evidence that young people who are at risk and who go on to develop major mood and psychotic disorders, often develop non-specific symptoms over time and development prior to the onset of the recognised disorder (41, 42). Current cross-sectional diagnostic symptoms which do not take familial risk and clinical course into consideration fail to recognise these stages. There is emerging evidence of identifiable clinical stages in the development of these disorders and clinical staging models have been proposed which may improve early identification and help to develop stage-specific treatments (41, 42). Anxiety and sleep problems often precede bipolar disorder, followed by adjustment and minor mood problems. The Amish study described symptom progression during development from anxiety to high levels of energy, sleep disturbance, excessive talking and problems with thinking and concentration; these symptoms also occurred in mini-clusters rather than being chronic, reflective of the episodic nature of BPD (40). The first diagnosable mood episode tends to occur by the age of 12, mostly bipolar disorder-NOS or major depression (37), prior to the peak onset of BPD, around late-adolescence. Thus the available evidence emphasises the importance of a developmental approach to the early identification of young people who may be at risk of developing bipolar disorder and an awareness of the early stages in the course of this disorder. Further work is, however, needed on describing these stages more accurately and developing treatments.

Pharmacological treatment

There have been relatively few studies of pharmacological treatment of BPD in young people (43). Published studies are problematic, as they include a limited number of RCTs, most of which have been small and in which treatment response rates have varied, partly as a result of inconsistent definitions of BPD and differing methodology. Existing guidelines are therefore largely extrapolated from adult data; the more classical a presentation, the more likely it is that adult guidelines will be applicable.

Medication remains the first-line treatment for cases of that meet diagnostic criteria (27), although caution should be used with pre-pubertal mania as the effectiveness and safety of medication has not yet been established in children (43). Medication should be prescribed by a specialist in child and adolescent psychiatry and, as this is a rapidly changing area, clinicians need to be aware of recent developments in prescribing and changes in licensing indications (www.medicines.org.uk/EMC/default.aspx). We have little data on the management of cases at high risk of developing BPD; psychosocial approaches remain first-line management in these young people.

Randomised controlled trials (RCTs)

Although lithium is generally considered to be the 'gold standard' treatment for bipolar disorder in adults and is an option for adolescent classical mania, more recent placebo-controlled trials for lithium in young people have had mixed findings (44, 45). A large lithium trial is currently underway (46). Placebo-controlled RCTs for divalproex have been negative in young people for both BPD and BPD spectrum (47, 48).

With regard to the second-generation antipsychotics (SGAs), one large placebo-controlled trial has been conducted involving adolescents with mania. This study demonstrated that olanzapine was effective but weight gain and metabolic adverse effects were a problem (49). There is some evidence from two small studies for the efficacy of quetiapine and risperidone in relation to divalproex (50, 51). In a large trial of children and adolescents with BPD-I, risperidone was superior to either lithium or divalproex; response rates between lithium and divalproex did not differ (52). Therefore, current evidence suggests that the SGAs are more effective than lithium or divalproex in acute mania, in contrast to adult data (53).
Little data is available on bipolar depression in young people, so treatment decisions are therefore made on a case-by-case basis. One small placebo-controlled study of quetiapine in bipolar depression has been negative in adolescents (54).

Guidelines

The NICE National Collaborating Centre for Mental Health guidelines recommend SGAs, rather than mood stabilisers, as a first-line treatment for acute mania, in cases meeting adult criteria (27). This recommendation is supported by the more recent trial data and Food and Drugs Administration (FDA) indications in the US (55).

In the UK, lithium carbonate remains the only medication licensed for BPD in young people from 12 years of age. Therefore, off-licence prescribing will need to be discussed with families for the majority of medications used. Lithium is generally not recommended for acute mania if symptoms are severe, in view of its slower onset of action. Regular blood monitoring is required, which is often not popular with young people. NICE advises against prescribing valproate in girls, owing to its possible association with polycystic ovarian syndrome. If an antipsychotic alone is ineffective, lithium or valproate are suggested as an augmentation strategy, and a benzodiazepine such as lorazepam can be used to manage agitation, if required. In the US, risperidone, quetiapine and aripiprazole have also been approved by the FDA from the age of 10, and olanzapine from age 13.

BPD may require lifelong treatment, although results from an 8 year longitudinal study of childhood BP-I (definitions adapted) would suggest that the majority of childhood cases will not meet criteria for manic episodes by age 18 and above (56). For those young people requiring longer-term treatment, there is little evidence to guide clinicians and consequently adult guidelines are used. One small study of lithium versus divalproex in maintenance treatment did not find a difference in relapse rates (57). NICE suggests the use of lithium, olanzapine or valproate, and either switching medications or using a second agent in the event of an inadequate response. Carbamazepine or lamotrigine are suggested if a trial of combined agents proves ineffective. However, there is minimal available data on their use in young people with BPD and their use is also not licensed in the US in this age group.
In practice, the choice of medication will be governed not only by guidelines but also the most recent evidence base, treatment response, willingness to comply with blood testing and adverse effect profile

(58). In view of the paucity of the evidence and concerns regarding potentially serious adverse effects, the risks and benefits of medication need to be considered carefully with the family. If medication is commenced, the principle is to 'start low, go slow', with closer monitoring than in adults.

Adverse effects

Children and adolescents appear to be at higher risk than adults for a number of adverse effects, such as extrapyramidal symptoms, metabolic effects and endocrine abnormalities (59). Although the SGAs carry a lower risk for extra-pyramidal side effects (EPS) than the first-generation antipsychotics (60), case reports exist for all of the SGAs. SGAs are associated with weight gain, type 2 diabetes, and dyslipidemias. The risk appears to be greatest with olanzapine, intermediate with quetiapine and risperidone, and low for aripiprazole (53, 60, 61). Young people are more susceptible to weight gain than adults (53). Risperidone is associated with the greatest risk for hyperprolactinemia, followed by olanzapine; aripiprazole is associated with reduced prolactin levels (60). Long-term anti-psychotic use in adults has been associated with brain tissue loss over time (62), suggesting the importance of a careful risk-benefit review of dosage and duration of treatment, particularly since the longer-term effects in young people are unclear. Although adverse events have usually been minor in the randomised studies of SGAs, longer-term open-label studies have indicated that some adverse events, such as the metabolic effects, may be severe and potentially life-threatening in the long term (63). Lithium needs to be carefully monitored for renal adverse effects and hypothyroidism, as well as for lithium intoxication. Valproate is highly teratogenic and increases the risk of polycystic ovary syndrome, with its associated symptoms of menstrual dysfunction, hirsutism and acne.

Psychosocial treatment

All medication prescribing should occur within a psychosocial therapeutic framework. Because academic, social and family functioning may all be affected, treatment needs to be multimodal; it should include liaison with other professionals and advice on relapse prevention (8). Components of psychosocial interventions should include advice on managing overactivity, sleep, diet, structured activities and psychoeducation, as well as increasing parental collaboration. Other components include helping parents distinguish between normal developmental behaviour and manic symptoms, managing emotional arousal, improving family communication and providing problem-solving strategies. Multi-family psychoeducation produces improvements over routine care (64) and functional family therapy is associated with more favourable outcomes for depressive symptoms (65).

The Role of the GP

Risk factors for longer episode duration include rapid cycling, psychotic symptoms, earlier age of onset, low socioeconomic status, comorbid anxiety, ADHD, and/or disruptive behaviour disorders and a negative parenting style, as well as nonadherence with pharmacological treatment (13).

GPs have an important role throughout the longitudinal course of this illness with regard to the following.
1. Early detection of young people at high risk of BPD (family history, recurrent low mood, non-specific impairing symptoms) and referral to CAMHS.

2. Early referral of young people to CAMHS with possible manic symptoms, particularly in those with a family history and recurrent depression. Psychotic symptoms would indicate an urgent need for specialist assessment.

3. Risk assessment and prompt referral to CAMHS of young people with suicidal thinking/behaviour.

4. Managing parents with BPD or other psychiatric disorders.

5. Awareness of safeguarding issues. One in five young people with BPD have experienced physical or

sexual abuse (66); child maltreatment and neglect is associated with suicidality and poorer outcomes (67).
6. Assessment for concurrent drug and alcohol use (17). Refer to appropriate agencies.

7. Family support and relapse prevention: psychoeducation, particularly regarding safe medication management, and need for medication adherence, since this is a major factor associated with relapse (11).

8. Need for physical monitoring with medication (in conjunction with specialist): healthy eating and exercise habits should be encouraged, with monitoring of weight, cardiac, renal, liver and thyroid function, and blood monitoring of glucose and lipids (68).

Conclusion

Although bipolar disorder is a relatively rare disorder in young people, it is a complex, high-risk condition which requires careful specialist management. The GP has a vital role throughout the course of this disorder, with regard to early detection, the management of physical health, risk identification and awareness of the psychosocial factors which may be contributing to the disorder.

GP Comment

What have I learned from this paper?

This an interesting article. However, there are unrealistic expectations of how much can be achieved within the 7-10minute GP consultation period. Perhaps a GP with special interest in psychiatry with 30 minute appointment slots might be an option but this could impact negatively on the other partners at the practice.

This makes good reading for difficult implementation

Dr Vishal Naidoo, GP.

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