The overlap of pervasive developmental disorders and bipolar disorder in young people

Mai Uchida, MD1,2, Emily Gray, MD1,2, and Gagan Joshi, MD1,2
1 Pediatric Psychopharmacology Program, Massachusetts General Hospital
2 Department of Psychiatry, Harvard Medical School
Boston, Massachusetts
Address of Corresonding Author
Gagan Joshi, MD. Clinical & Research Programs in Pediatric Psychopharmacology, Massachusetts General Hospital, 55 Fruit Street, YAW 6900, Boston MA 02114
Email: Joshi.Gagan@MGH.Harvard.edu

Abstract

Recent research has proved the bidirectional relationship between pervasive developmental disorders (PDD) and bipolar disorder (BPD). Young people with BPD comorbid with PDD present with earlier onset and higher severity of mood disturbance, and young people with PDD with family history of BPD present with mood disturbance characterized by a severe cycling pattern and agitation along with neurovegetative disturbances. Treatment approaches include similar comprehensive psychosocial interventions targeting PDD symptomatology with the addition of psychopharmacological interventions to target comorbid mood symptoms. This population is more prone to adverse effects and can have an atypical response to psychoactive medications; it is recommended that medication be initiated at a low dose and titrated in small increments. Second-generation antipsychotics are effective with both the consequences of the PDD (aggression and irritability) and the comorbid mania but also carry the concerning adverse effects of weight gain and impaired glucose metabolism.

Key words: pervasive developmental disorder, bipolar disorder, comorbidity, young people, clinical correlates.

Pervasive Developmental Disorders

Pervasive developmental disorders (PDD) are characterized by delays in development of socialization and communication, and include diagnoses such as autism, Asperger Syndrome and Pervasive Developmental Disorder not otherwise specified. Children with PDD present with symptoms such as difficulty relating to people (lack of eye contact, unresponsive to social cues such as smiles and body language), difficulty communicating with or without language, limited range of interests which may involve unusual play, difficulty with change in routine, and repetitive behaviour patterns. Autism spectrum disorders (ASD) are estimated to affect more than 1% of children and adolescents in the general population (1). Since these children often have excessive anxiety and mood lability, the co-occurrence of mood disorders and other psychiatric disorders must be carefully investigated.

Bipolar disorder in children

Both autism spectrum disorders (ASD) and pediatric bipolar disorder (BPD) are severely impairing chronic conditions. Each disorder affects at least 1% of the pediatric population (2). It is reported that mood disturbance in children with BPD is often characterized by mixed features of depression and mania. These children commonly present with extreme irritability, explosiveness, abrupt changes in mood states from angry to giddy, and occasional periods of low energy and withdrawal.

Comorbid pervasive developmental disorders and bipolar disorder

The existence of an overlap of BPD and PDD has been suggested by clinicians prior to the recent growth of literature in this topic, since children with PDD presented with high rates of aggressive

behaviours and labile mood. The high incidence of BPD in family members of children with PDD had also been noticed.

An accumulating body of literature has demonstrated that there are high rates of aggressive behaviours and mood disturbances in children with PDD that indeed qualify for diagnoses of affective disorders including BPD (3-12). Conversely, high rates of PDD or PDD traits have been reported in children and adolescents with BPD. One study reported that in children with mood and anxiety disorders, PDD traits can be found in as many as 62% (8).

A bidirectional relationship

In our study, we assessed children and adolescents using a comprehensive diagnostic battery and structured diagnostic interview. We found a bidirectional relationship: BPD occurred in 21% of PDD, and PDD occurred in 11% of BPD young people (8). In another study, we administered a structured diagnostic interview to children with PDD in our clinic, and we were able to diagnose one-third of them with also BPD (11). Similarly, we found 15% comorbidity of PDD in the research population of children with BPD (11,12).

Characteristics of children with comorbid PDD and BPD

The clinical characteristics of PDD and BPD were strikingly similar irrespective of the comorbidity (11). On CBCL profile reported by parents, significantly worse behavioural difficulties were found in BPD young people in the presence of PDD (13). Furthermore, when comorbid with PDD, children and adolescents with BPD present with an earlier onset, increased severity of mood disturbance and poorer level of functioning (11-13). Young people with a PDD diagnosis with family history of BPD often present with mood disturbance characterized by a severe cycling pattern and agitation, along with neurovegetative disturbances (14). There is also a growing body of literature from family genetic studies suggesting higher incidence of BPD in first-degree relatives in PDD population (14–16).

Treatment

Treatment of children with PDD is complex and involves coordinating care through multiple domains of services including: psychotherapy, social skills training, speech and language intervention, occupational and physical therapy, vocational training, and psychopharmacologic interventions to target impairing symptoms of comorbid psychiatric disorders. The remainder of the discussion will focus on the treatment of the comorbid bipolar disorder through pharmacological means.

Pharmacological treatment considerations

An important concern, with regard to the PDD population, is that treatment response to psychotropic medication is noted to be less robust and with higher rates of adverse effects to both medication and placebo (17-19). Therefore, due to an atypical response and higher susceptibility to adverse effects, it is advisable to "start low and go slow," initiating psychotropics at a lower dose and titrating upward in smaller increments in this population. Despite substantial evidence documenting the role of pharmacotherapy for the management of extreme mood difficulties, there is a paucity of published literature, with limited controlled trials regarding psychoactive medications for the treatment of comorbid BPD in this population and, therefore, psychopharmacological treatment approaches should be made judiciously with patients being closely monitored for treatment effects (adverse effects and symptom improvement).

The limited literature on the treatment of comorbid BPD in children with PDD suggests that first-generation antipsychotics (haloperidol, chlorpromazine, thioridazine) and traditional mood stabilizers (lithium, carbamazepine) are minimally effective as monotherapy for the treatment of mania (20). Although there are few studies of lithium within the PDD population, case reports indicate that lithium may be helpful in combination with neuroleptics or other antimanic medications (20). In a

recent secondary analysis of acute second-generation antipsychotic monotherapy trials in BPD young people, we reported acceptable tolerability and robust antimanic response to atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) in the presence of PDD comorbidity (10). There were no differences observed in the rate of antimanic response and tolerability, with the exception that PDD young people were more susceptible to the adverse effect of slurred speech and teary eyes. Furthermore, compared with other atypical antipsychotics, risperidone produced a superior antimanic response in BPD young people with comorbid PDD. However, this study was limited by the retrospective nature of post hoc analysis and lack of direct measures of PDD symptomatology.

There is evidence from the treatment trials of risperidone, aripiprazole, and ziprasidone that second-generation neuroleptics are also well tolerated and effective in treating symptoms of irritability and aggression in young people with PDD, a spectrum of symptoms suggestive of BPD. Controlled trials of risperidone consistently report favourable safety, tolerability and efficacy profiles for treating symptoms of irritability and aggression in young people with PDD (21-23). Although risperidone is the only atypical antipsychotic that the United States Food and Drug Administration has approved for the treatment of irritability and aggression in autistic children, weight gain associated with risperidone is a significant adverse effect that often limits continuation of treatment in this population. In contrast, results from recent short-term open trials with the newer atypical antipsychotics aripiprazole and ziprasidone show promise as a treatment for irritability in children with PDD and are associated with negligible weight gain (24,25). Contrary to the encouraging response observed with the aforementioned atypical antipsychotics, the atypical antipsychotics quetiapine and olanzapine are noted to be ineffective in treating symptoms of irritability and aggression in this population 26-28).

Therefore, when selecting a thymoleptic agent for the treatment of BPD in young people with comorbid PDD, attention should be given to those antimanic agents that are also shown to be effective in treating associated and core features of PDD. Furthermore, in this population, due to higher susceptibility to adverse effects, as mentioned above, it is advisable to initiate and titrate psychotropics at a lower dose. As the aforementioned empiric evidence suggests, risperidone appears to be effective in treating both core and associated features of PDD and may be superior to other atypical antipsychotics as an antimanic agent in young people with PDD. Young people should be monitored closely for adverse effects, especially weight gain, as this remains a concern in short-term and long-term therapy with risperidone. Recent studies have investigated the use of metformin to mitigate weight gain and abnormal glucose metabolism secondary to the use of second-generation antipsychotics. These studies have shown a positive effect for metformin use in children, but failed to produce similar results in adults (29, 30). With regard to evidence for the effect of metformin on mitigating weight gain secondary to antipsychotic use in the PDD population, there are only case reports (31).

Conclusion

Within the PDD population, there is a high prevalence of comorbid psychiatric conditions. There is an overlap in symptomatology between PDD and BPD that presents diagnostic challenges; a growing literature demonstrates that there is a bidirectional relationship between the two conditions. Severe behavioural disturbance and poor level of functioning are found in the young people with comorbid PDD and BPD. Identifying comorbid BPD in individuals with PDD is crucial so that these children can receive appropriate treatment. Within the limited studies, second-generation antipsychotics as monotherapy show promising responses. However, the success of these medications is diminished with the concerns about the adverse-effect profile of weight gain and impaired glucose metabolism; these appear to be more common in children. Additional studies have investigated the use of metformin to mitigate the metabolic adverse effects of antipsychotics with conflicting results. With the paucity of literature that has systematically evaluated psychopharmacological treatment of comorbid BPD and PDD, there continues to be a gap in our understanding of the full risks and benefits of treatment. There is a need for further rigorous investigation.

GP Comment

What have I learned from this paper?

1. There is an overlap of symptoms between bipolar disorder and autism spectrum disorder; there appears to be a bidirectional relationship between the two diagnoses.

2. The limited evidence seems to suggest that risperidone could be useful for treating both conditions but concerns about weight gain and the risk of diabetes imply that close monitoring is required.

3. Because of the complexities around both diagnosis and treatment, if I suspected that an individual had both bipolar disorder and autism spectrum disorder, I would refer to a specialist psychiatrist for management.

Dr Mayruja Santhirakumar, GP Trainee.

References

1. Autism and Developmental Disabilities Monitoring Network. Prevalence of Autism Spectrum Disorders. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report; March 30 2012.
2. Geller B, Fox L, Clark K. Rate and predictors of prepubertal bipolarity during follow-up of 6-to 12-year-old depressed children. J Am Acad Child Adolesc Psychiatry 1994; 33: 461-8.
3. Joshi G, Wilens T. Comorbidity in pediatric bipolar disorder. Child Adolesc Psychiatr Clin N Am 2009; 18 (2): 291-319.
4. Kerbeshian J, Burd L. Case study: comorbidity among Tourette's syndrome, autistic disorder, and bipolar disorder. J Am Acad Child Adolesc Psychiatry 1996; 35: 681-5.
5. Komoto J, Seigo U, Hirata J. Infantile autism and affective disorder. J Autism Dev Disord 1984; 14: 81-4.
6. Sovner R, Hurley AD. Do the mentally retarded suffer from affective illness? Arch Gen Psychiatry 1983; 40: 61-7.
7. Steingard R, Biederman J. Lithium responsive manic-like symptoms in two individuals with autism and mental retardation. J Am Acad Child Adolesc Psychiatry 1987; 26: 932-5.
8. Wing L. Asperger's syndrome: a clinical account. Psychol Med 1981; 11: 115-29.
9. Towbin KE, Pradella A, Gorrindo T et al. Autism spectrum traits in children with mood and anxiety disorders. J Child Adolesc Psychopharmacol 2005; 15: 452-64.
10. Wozniak J, Biederman J, Faraone S et al. Mania in children with pervasive developmental disorder revisited. J Am Acad Child Adolesc Psychiatry 1997; 36: 1552-60.
11. Joshi G, Petty C, Wozniak J, Henin A, Fried R, Galdo M, Kotarski M, Walls S, Biederman J. The heavy burden of psychiatric comorbidity in youth with autism spectrum disorders: a large comparative study of a psychiatrically referred population. J Autism Dev Disord 2010 Nov; 40 (11): 1361-70. PMID: 20309621.
12. Joshi G, Biederman J, Wozniak J, Doyle R, Hammerness P, Galdo M, Sullivan N, Williams C, Brethel K, Woodworth KY, Mick E. Response to second generation antipsychotics in youth with comorbid bipolar disorder and autism spectrum disorder. CNS Neurosci Ther 2012 Jan; 18 (1): 28-33 PMID: 21114638.
13. Joshi G, Biederman J, Petty C, Goldin R, Wozniak J. Examining the Comorbidity of Bipolar Disorder and Autism Spectrum Disorders: A Large Controlled Analysis of Phenotypic and Familial Correlates in Referred Population of Youth with Bipolar I Disorder with and without Autism Spectrum Disorders. J Clin Psych (accepted for publication).
14. DeLong GR, Nohria C. Psychiatric family history and neurological disease in autistic spectrum disorders. Dev Med Child Neurol 1994; 36: 441-8.
15. DeLong GR, Dwyer JT. Correlation of family history with specific autistic subgroups: Asperger's syndrome and bipolar affective disease. J Autism Dev Disord 1988; 18: 593-600.
16. Herzberg B. The families of autistic children. In: Coleman M (ed.) The autistic syndromes.

Amsterdam: North Holland; 1976. p 151-72.
17. Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry 2005; 62: 1266.
18. Aman MG, Arnold MDL, McDougle CJ et al. Acute and long-term safety and tolerability of risperidone in children with autism. J Child Adolesc Psychophar- macol 2005; 15: 869-84.
19. Posey DJ, Wiegand RE, Wilkerson J et al. Open-label atomoxetine for attention- deficit/hyperactivity disorder symptoms associated with high-functioning pervasive developmental disorders. J Child Adolesc Psychopharmacol 2006; 16: 599-610.
20. Lainhart JE, Folstein SE. Affective disorders in people with autism: a review of published cases. J Autism Dev Disord 1994; 24: 587-601.
21. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002; 347: 314-21.
22. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo controlled, double-blind study. J Child Neurol 2006; 21: 450-5.
23. Shea S, Turgay A, Carroll A et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics 2004; 114: e634-41.
24. Malone RP, Delaney MA, Hyman SB et al. Ziprasidone in adolescents with autism: an open-label pilot study. J Child Adolesc Psychopharmacol 2007; 17: 779-90.
25. Stigler KA, Diener JT, Kohn AE et al. A prospective open-label study of aripiprazole in youth with Asperger's disorder and pervasive development disorder not otherwise specified. Neuropscyhopharmacology 2006; 31: S194.
26. Findling RL, McNamara NK, Gracious BL et al. Quetiapine in nine youths with autistic disorder. J Child Adolesc Psychopharmacol 2004; 14: 287-94.
27. Hollander E, Wasserman S, Swanson EN et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. J Child Adolesc Psychopharmacol 2006; 16: 541-8.
28. Martin A, Koenig K, Scahill L et al. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 1999; 9: 99-107.
29. Klein DJ, Cottingham EM, Sorter M et al. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. Am J Psychiatry 2006; 163: 2072-2079.
30. Bapista T, Martinez J, Lacruz A et al. Metformin for prevention of weight gain and insulin resistance with olanzapine: A double-blind placebo-controlled trial. Can J Psychiatry-Revue Canadianne de Psychiatrie; 2006; 51: 192-196.
31. Gutkovich ZA, Carlson GA, Carlson HE et al. Advanced Pediatric Psychopharmacology: Asperger's disorder and co-morbid bipolar disorder: Diagnostic and treatment challenges. J Child Adolesc Psychopharmacol 2007; 17: 247-255.