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Comorbidity of bipolar disorder and autism spectrum disorder – review paper

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Summary

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders that can affect up to 2.6% of the population. Most of these people will have at least one other psychiatric disorder, often diagnosed with a delay or not recognized at all. This study describes the epidemiology, diagnostic difficulties and potential treatment of patients with ASD and comorbid bipolar disorder (BD). The prevalence of bipolar disorder in ASD is estimated at 5–8%. The study with the most numerous group included 700,000 children out of which 9,062 fulfilled ASD criteria at 16 – BD was found to be 6 times more prevalent in this group compared to the control group. Many factors affect the diagnosis. Patients with ASD often have limited insight into understanding the complex emotional states and difficulty in expressing them due to their impairment. The symptoms of bipolar disorder are in their case unspecific and differ from those occurring in the general population, which makes it difficult to make proper diagnosis. Despite the lack of research on the group of patients with ASD, psychometric tools designed to evaluate the general population are used to examine patients. This work aims to show the current state of knowledge and highlight areas that require further investigation

Key words: bipolar disorder, autism spectrum disorder, comorbidity

Introduction

Autism spectrum disorders (ASD) is a heterogenic group of neurodevelopment impairments that begins in early childhood and affects mainly boys [1]. According toDSM-5, two main groups of symptoms prevalent in ASD are persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests or activities [2]. DSM-5 classification no longer distinguishes separate nosological entities (such as Asperger's syndrome, atypical autism and childhood

autism) but distinct three levels of severity of ASD. Additionally, previous name of this group, still used in ICD-10 classification – "pervasive developmental disorders" (PDD) was changed to autism spectrum disorder (ASD). Studies on large groups of patients report that this type of impairment may affect from 2.2% of children population up to 2.6% depending on the place where the study was conducted [3, 4]. Most people with ASD develop at least one additional psychiatric disorder during their lifetime. Oftentimes this disorder remains untreated due to patient's difficulty with communicating their emotions [5].

Considering all this the challenge of proper diagnosis and treatment of ASD comorbidities is dire and requires further research. This study presents current knowledge regarding ASD and bipolar disorder (BD) comorbidity. Bibliography for this article was created using Pubmed database, searching the key words through articles from 1984 to 2018: autism, autism spectrum disorder, ASD, Asperger's syndrome, bipolar disorder, BD, comorbidity.

BD is a disorder characterized by manic or depressive episodes that can be intersected by remissions [2]. Proper evaluation of the patient's emotional state is the key to properly diagnose and treat patients with BD and that is, as this article will show, incredibly difficult while ASD comorbidity is present. Accurate diagnosis and treatment of patients with BD and ASD should be regarded as an important challenge for the clinician due to the fact that it affects the patients functioning markedly. Therefore, awareness of this problem should be increased among physicians.

Epidemiology

First research that showed the possibility of both of these disorders occurring simultaneously was the one conducted by Janet Wozniak et al. [6]. A group of 727 people was described in which 52 individuals had only a PDD diagnosis, 114 – only manic episode and 14 patients had both manic episode and PDD, which was 21% of all PDD patients in this study. The literature shows many discrepancies regarding frequency of this disorders comorbidity. In the cohort study conducted by Selten et al. [7], which examined a population of almost 700 thousand children (the inclusion criteria were age below 17 years) through 11 years, 9,062 patients were diagnosed with ASD before the age of 16, and 10,726 patients –before the age of 28. In the group with diagnosis before the age of 16, 0.6% of patients were also given a BD diagnosis, while in the control group, consisting of 90,620 children, it was only 0.1%. In the group with diagnosis before the age of 28, 128 patients with ASD (0.11%) fulfilled criteria for BD. Adjusted OR (odds ratio) of developing BD was 6.6 times higher in patients with ASD compared to their healthy peers before the age of 28 and 4.3 times higher for the group with diagnosis before the age of 16 compared to controls [7]. Interestingly, ASD patients that placed above 3rd percentile for parameters regarding school performance suffered from comorbid BD more often than their peers who functioned poorer. The authors considered better understanding of the illness and limitations it

brings in people with higher IQ as the reason for this phenomenon – it can be seen as a factor in developing a depressive episode, but they do not explain how it may contribute to developing a manic episode.

Rosenberg et al. [8] put on a different thesis and associated higher rate of BD in patients with higher intellect with the fact that the affective comorbidity is easier to spot due to more typical course of illness and the fact that these patients communicate more easily. In their study, 5.2% of 4,343 patients with ASD had been given BD diagnosis and it placed as 3rd (after ADHD and anxiety disorder) most common comorbidity. Male gender was associated with higher risk of all these comorbidities.

Joshi et al. [9] compared 217 patients with ASD with a group of 217 persons, matched for age and gender, from the same center, that did not have neurodevelopmental impairment. This study showed no statistically significant differences regarding BD frequency in the ASD group compared to the patients without developmental disorders (the percentage was 31% and 30%, respectively). It is important to note that in some studies the comorbidity percentage is much lower – for example, the study by Ståhlberg et al. from 2014 [10], where only 9 (7%) out of 129 ASD patients had BD diagnosis. Lugnegård et al. [11] in their study reported that 9% (5 out of 54) of patients suffering from Asperger's syndrome (AS) had comorbid BD. It must be addressed that AS is just a part of ASD and this finding cannot be extrapolated onto the whole ASD group. In the study by Gjevik et al. [12], none of the 71 ASD patients fulfilled the criteria for BD.

Outcome similar to this of Wozniak et al. [6] was demonstrated by Weissman and Bates [13] – in their study, 11 out of 76 (14.5%) patients with ASD had comorbid BD and, additionally, 10 (12.1%) patients fulfilled criteria for a subclinical type of this disorder. In the study by Munesue et al. [14], out of 44 highly functioning ASD patients (IQ >70, older than 12 years and under psychiatric observation) 12 (27%) were diagnosed with BD [14].

In a 2015 review study [5], authors gathered 20 original publications from years 1997–2013 that focused on ASD and BD comorbidity [15]. It showed a discrepancy – the comorbidity varied from 0.74% up to 56.9%. Study that showed the highest comorbidity was conducted on population with BD diagnosis that was screened for ASD. Authors, on the basis of their research, estimate real comorbidity of ASD and BD to be approximately 7%.

Such discrepancy suggests the need for further population-based studies to help discover the real frequency of comorbidity of BD in ASD.

Diagnosis

The assessment of the comorbidity of autism spectrum disorders and bipolar disorder is interfered by both the diagnostic limitations resulting from the specificity of both these disorders, as well as by the possibility of changing their course in a situation of simultaneous occurrence. Both types of disorders persist from childhood to adulthood, however, their expression varies depending on the age of patients. In the

case of adult patients, autism spectrum disorders are often not properly diagnosed for a long time, which results from differences in the severity of symptoms in individual patients as well as their misinterpretation [16]. In addition, the heterogeneity of the disorders included in this spectrum is a diagnostic challenge even for an experienced psychiatrist [17].

Not without significance is the fact that characteristic ASD symptoms (such as abstract thinking difficulties, limited emotional expression, poor verbal and non-verbal communication skills) significantly limit the ability to identify the main symptoms of affective disorders in this group of patients [18–20]. Due to the fact that patients with ASD may display difficulties in describing their emotional states, clinical information about their health condition is often derived from family members or from the observation of a patient in a social environment [21]. Moreover, symptoms typical of ASD may mask or distort the psychopathological manifestations of other disorders and thus make their diagnosis difficult. It has been shown that people with ASD are extremely sensitive to minor environmental changes and often respond to them by sudden mood swings. Such kind of fluctuations in the emotional state of the patient may imitate or mask the comorbid affective disorder [22, 23]. Due to the difficulty in modulating and controlling the state of arousal, any change in the routine or a new social situation can become a factor provoking a number of symptoms such as: irritation, emotional hyper-reactivity, psychomotor agitation, and insomnia, which are easily misinterpreted as an affective episode [21, 24, 25]. Noteworthy is the fact that for the evaluation of people with the described type of disorders psychometric tools designed to evaluate the general population are used, whose diagnostic accuracy was not assessed in the group of people with ASD, which questions the validity of their use in the aforementioned group of patients.

Most of the studies describing the coexistence of ASD with other disorders are based on the demonstration of the presence of symptoms typical for the studied disorder without attempting to refer them to the course of ASD. An example of this can be the attempt to diagnose BD basing on the finding of the presence of manic and hypomanic episodes, which are difficult to define and confirm in people with ASD. Such an approach, therefore, forces us to consider whether the traditional assessment provides reliable results, and whether the diagnostic criteria and the diagnostic tools derived from them should not be re-evaluated and adapted to the needs of the group of patients with ASD [21].

An additional problem are the differences in the clinical picture and the course of bipolar disorder in children and adolescents. It is thought that due to the lack of a uniform definition of this disorder for the age group of children, the number of patients is probably higher than the number of people diagnosed properly. Moreover, during childhood and early adolescence BD is expressed by clinical symptoms of unipolar affective disorder, acute psychosis or conduct disorders, and symptoms of mania are revealed in later years of its duration [16]. In the group of adolescents with co-occurring BD and ASD, racing thoughts, distractibility, depressed mood, social withdrawal, and

low reactivity of negative mood states are frequently found. These patients present a typical clinical picture of BD, however, with earlier onset of symptoms, mixed presentation of symptoms and the occurrence of additional functional impairment, with symptoms tending to reduce their severity over time [26]. On the other hand, it has been shown that BD in ASD adults is often initially erroneously diagnosed as schizophrenia, which results from atypical presentation of mood swings and differences in behavior of patients during periods of mood stabilization [27, 28].

In patients with ASD, mania takes an unusual picture due to the dominance of increased irritation, emotional instability and dysphoria in this period. Hostile, aggressive and violent behavior, anxiety and consternation are also found, while typical mania features such as euphoric mood are less common [16, 20, 28–31]. In many cases, making a correct diagnosis is additionally hampered by a particular severity of psychotic symptoms [16, 28, 30, 31]. Among described patients, bizarre thoughts, often interpreted as delusions, are also found during manic episodes, but they should be differentiated with the specific way of thinking of people with ASD, also occurring during euthymic periods [31–34].

It is also challenging to determine the occurrence of depressive episodes in people with ASD, as their symptoms usually have a mild and long-lasting course in these patients. Due to their image, as well as social consequences, there is a risk of their misinterpretation as interpersonal difficulties or poor emotional expression typical for ASD [28]. However, in patients with ASD, as often as in the case of other people, symptoms typical for depression, such as anhedonia, reduced drive, depressed mood, suicidal thoughts, difficulty in concentration and decision making, and somatic symptoms occur [35–38]. Similarly as in the case of mania, depressive episode in people with ASD may be accompanied by symptoms of irritation, rapid emotional lability, self-aggression, aggression against the environment, and excitement, which requires careful assessment of the patient for a correct diagnosis [23, 37–40].

In people with ASD, it is particularly difficult to differentiate between episodic mood changes and responses to deviations from daily routines, negative life events or changes in the environment. Therefore, it is problematic to confirm the 'self-existence' of the affective episode, especially in the initial stage of the disorder. It was also observed that the symptoms of bipolar disorder may influence directly the course of ASD, exacerbating the impairment of social and cognitive functioning, especially in adolescents with disorders of this spectrum [13]. The worsening of the main symptoms of ASD by BD, thus modifies the typical clinical picture of a patient with pervasive developmental disorders [20, 41]. Often, the principal symptoms of an affective episode can be a sudden increase in ASD main symptoms in a previously well-functioning patient.

In conclusion, the atypical course of bipolar disorder as well as diagnostic difficulties in identifying ASD and the phenomenon of mutual masking and distortion of symptoms by co-occurring disorders make it difficult to diagnose affective disorders in people with ASD [13]. Therefore, it would be beneficial to create customized

diagnostic tools and apply the appropriate clinical approach to the analysis of such cases. In Table 1, we summarized the differences in the clinical picture of individual symptoms of a manic episode in people with ASD.

Table 1. **Atypical presentation of manic symptoms according to ICD-10 in people with PDD [42]**

BD	ASD + BD
Mood elevated or irritable to an extent definitely abnormal for a given person, persisting for at least a week	
There are at least 3 of the following symptoms, leading to a dysfunction of individual functioning in everyday life:	
Increased activity or physical anxiety	Aggravation of motor stereotypies, self-aggressive behavior
More talkative than usual	Fast, loud and more frequent sounding in people with impaired speech development
Flight of ideas or subjective experience that thoughts are racing	Difficult to assess due to communication difficulties
Loss of normal social inhibitions, leading to behaviors inadequate to the circumstances	Difficult to assess due to the typical for autism occurrence of socially inappropriate behaviors. Possible aggressive, rebellious behavior, irritability
Reduced need for sleep	Difficult to assess due to primary sleep disturbances in ASD
Increased self-esteem or sense of superiority	Aggressive behavior, irritability
Easy distraction of attention or permanent changes in activities or plans	Frequent initiation of ritualized activities and failure to perform them
Reckless behavior with undervaluation of risk	Difficult to assess due to frequent undervaluation of risk in ASD and difficulty in causal thinking
Increased sexual energy	Periodic intensification of sexual behavior

Treatment

Currently, the use of pharmacotherapy in patients with comorbid BD and ASD is insufficiently studied. Literature is inconsistent and constituted mainly by case reports. The decision to apply treatment is problematic because of difficulties in diagnosing BD in patients with ASD resulting from the limitations described above. However, unrecognizing the comorbid BD may lead to inadequate treatment or delusive conclusion that mood stabilizers, antiepileptics, atypical antypsychotics or antidepressants are partially effective in ASD [16].

Lithium

Many authors support the efficacy of lithium compounds in patients with ASD, mood instability and cyclically repetitive behavioral disorders [43–46]. According to Lainhart et al. [23] in 5 out of 6 cases of patients with pervasive developmental disorders and mania, lithium monotherapy is ineffective and requires the addition of another drug. Lithium seems to be effective in patients with ASD and familial prevalence of BD, hyperactivity non-responsive to psychostimulants or cyclical behavioral disorders [45]. In a retrospective study of 30 children and adolescents diagnosed with ASD and comorbid mood disorders, 13 patients who received lithium improved on the CGI [47].

Antiepileptics

The efficacy of valproate has been described in patients with: ASD, mental retardation and BD, including rapid cycling [48]. In 10 of the 14 ASD patients, valproate was effective regarding mood instability, aggression and impulsivity [49]. Carbamazepine was effective in stabilizing mood in a 13-year-old patient with ASD [50]. In case reports [16], the use of oxcarbazepine and atypical neuroleptics in low doses shows good effectiveness in the treatment of comorbid Asperger's syndrome and BD.

Atypical neuroleptics

There are many reports on the use of neuroleptics in people with ASD, however, they refer to small populations, and the effectiveness of these drugs is described mainly in relation to behavioral disorders, without specifying the problem of BD coexistence [27]. Among the second-generation antipsychotics, risperidone and aripiprazole represent the only ones with FDA approval for use in the treatment of behavioral disorders occurring in ASD. Data from identically designed, 8-week studies with an open-label trial with the administration of various atypical neuroleptics in monotherapy were subjected to secondary analysis. 23 out of 151 BD patients, met the criteria of ASD. There was no significant difference in response to treatment with atypical neuroleptics between the group with and without comorbid ASD (69% of patients with BD and 65% of patients with BD and ASD presented an improvement of at least 30% at the YMRS (Young Rating Scale for Mania) and at least 2 points according to the CGI-Improvement scale)[51].

Conclusions

ASD and BD comorbidity requires further research, especially in large groups of patients.. Based on available literature, estimated prevalence of this phenomenon affects around 7% of ASD patients. Keeping in mind that number of people with diagnosis of ASD is steadily growing, it allows us to predict, that comorbidity of ASD with bipolar disorder is going to be a more common issue in psychiatric practice.

Correct diagnosis of those two disorders is impeded due to multiple factors. Main ones include: difficulties in communicating emotions, impaired insight into one's emotional state in patients with ASD, atypical clinical symptoms in case of comorbidity, and absence of tools adjusted typically for this group of people.

Proper identification of BD comorbidity is crucial. Without it, inadequate treatment may be prescribed. As of now no, randomized trials were conducted to determine which treatment is the most effective, but current literature suggests using atypical neuroleptics or antiepileptic drugs and lithium therapy as an alternative.

References

1. Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators. Centers for Disease Control and Prevention (CDC). *Prevalence of autism spectrum disorder among children aged 8 years – Autism and developmental disabilities monitoring network, 11 sites, United States, 2010*. MMWR Surveill. Summ. 2014; 63(2): 1–21.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 5th ed., rev. (DSM-5). Washington, DC: American Psychiatric Association; 2013.
3. Zablotsky B, Black LI, Maenner MJ, Schieve LA, Blumberg SJ. *Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 National Health Interview Survey*. Natl. Health Stat. Report. 2015; (87): 1–20.
4. Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC et al. *Prevalence of autism spectrum disorders in a total population sample*. Am. J. Psychiatry. 2011; 168(9): 904–912.
5. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. *Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample*. J. Am. Acad. Child Adolesc. Psychiatry. 2008; 47(8): 921–929.
6. Wozniak J, Biederman J, Faraone SV, Frazier J, Kim J, Millstein R et al. *Mania in children with pervasive developmental disorder revisited*. J. Am. Acad. Child Adolesc. Psychiatry. 1997; 36(11): 1552–1560.
7. Selten JP, Lundberg M, Rai D, Magnusson C. *Risks for nonaffective psychotic disorder and bipolar disorder in young people with autism spectrum disorder: A population-based study*. JAMA Psychiatry. 2015; 72(5): 483–489.
8. Rosenberg RE, Kaufmann WE, Law JK, Law PA. *Parent report of community psychiatric comorbid diagnoses in autism spectrum disorders*. Autism Res. Treat. 2011; 2011: Article ID 405849. Doi: 10.1155/2011/405849.
9. Joshi G, Petty C, Wozniak J, Henin A, Fried R, Galdo M et al. *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; 40(11): 1361–1370.
10. Stahlberg O, Soderstrom H, Rastam M, Gillberg C. *Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset ADHD and/or autism spectrum disorders*. J. Neural. Transm. 2004; 111(7): 891–902.
11. Lugnegård T, Hallerbäck MU, Gillberg C. *Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome*. Res. Dev. Disabil. 2011; 32(5): 1910–1917.

12. Gjevik E, Eldevik S, Fjæran-Granum T, Sponheim E. *Kiddie-SADS reveals high rates of DSM-IV disorders in children and adolescents with autism spectrum disorders*. J. Autism Dev. Disord. 2011; 41–41(6): 761–769.
13. Weissman A, Bates M. *Increased clinical and neurocognitive impairment in children with autism spectrum disorders and comorbid bipolar disorder*. Res. Autism Spectr. Disord. 2010; 4(4): 670–680.
14. Munesue T, Ono Y, Mutoh K, Shimoda K, Nakatani H, Kikuchi M. *High prevalence of bipolar disorder comorbidity in adolescents and young adults with high-functioning autism spectrum disorder: A preliminary study of 44 outpatients*. J. Affect. Disord. 2008; 111(2–3): 170–175.
15. Skokauskas N, Frodl T. *Overlap between autism spectrum disorder and bipolar affective disorder*. Psychopathology. 2015; 48(4): 209–216.
16. Raja M, Azzoni A. *Comorbidity of Asperger's syndrome and bipolar disorder*. Clin. Pract. Epidemiol. Ment. Health. 2008; 4: 26.
17. Frith U. *Emanuel Miller lecture: Confusions and controversies about Asperger syndrome*. J. Child Psychol. Psychiatry. 2004; 45(4): 672–686.
18. Damore J, Stine J, Brody L. *Medication-induced hypomania in Asperger's disorder (letter)*. J. Am. Acad. Child Adolesc. Psychiatry. 1998; 37(3): 248–249.
19. Eisenmajer R, Prior M, Leekam S, Wing L, Gould J, Welham M et al. *Comparison of clinical symptoms in autism and Asperger's disorder*. J. Am. Acad. Child Adolesc. Psychiatry. 1996; 35(11): 1523–1532.
20. Frazier JA, Doyle R, Chiu S, Coyle JT. *Treating a child with Asperger's disorder and comorbid bipolar disorder*. Am. J. Psychiatry. 2002; 159(1): 13–21.
21. Mazzone L, Ruta L, Reale L. *Psychiatric comorbidities in Asperger syndrome and high functioning autism: Diagnostic challenges*. Ann. Gen. Psychiatry. 2012; 11(1): 16.
22. Duggal HS, Dutta S, Sinha VK. *Mood stabilizers in Asperger's syndrome*. Aust. N Z J. Psychiatry. 2001; 35(3): 390–391.
23. Lainhart JE, Folstein SE. *Affective disorders in people with autism: A review of published cases*. J. Autism Dev. Disord. 1994; 24(5): 587–601.
24. Leibenluft, E. *Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths*. Am. J. Psychiatry. 2011; 168(2): 129–142.
25. Leibenluft E, Charney DS. Towbin KE, Bhangoo RK, Pine DS. *Defining clinical phenotypes of juvenile mania*. Am. J. Psychiatry. 2003; 160(3): 430–437.
26. Borue X, Mazefsky C, Rooks BT, Strober M, Keller MB, Hower H et al. *Longitudinal course of bipolar disorder in youth with high-functioning autism spectrum disorder*. J. Am. Acad. Child Adolesc. Psychiatry. 2016; 55(12): 1064–1072.
27. Vannucchi G, Masi G, Toni C, Dell'Osso L, Erfurth A, Perugi G. *Bipolar disorder in adults with Asperger 's Syndrome: A systematic review*. J. Affect. Disord. 2014; 168: 151–160.
28. Skeppar P, Thoor R, Sture A, Isakson A, Skeppar I, Persson B et al. *Neurodevelopmental disorders with comorbid affective disorders some-times produce psychiatric conditions traditionally diagnosed as schizophrenia*. Clin. Neuropsychiatry. 2013; 10(3–4): 123–133.
29. Joshi G, Biederman J, Petty C, Goldin RL, Furtak SL, Wozniak J. *Examining the comorbidity of bipolar disorder and autism spectrum disorders: A large controlled analysis of phenotypic and familial correlates in a referred population of youth with bipolar I disorder with and without autism spectrum disorders*. J. Clin. Psychiatry. 2013; 74(6): 578–586.

30. Ng B, Au M, Verhoeven M, Johnston L, Perkins C. *The diagnosis of Asperger's syndrome in an adult presenting with an index episode of mania*. Gen. Hosp. Psychiatry. 2003; 25(4): 295–297.
31. Raja M, Azzoni A. *Thought disorder in Asperger syndrome and schizophrenia: Issues in the differential diagnosis. A series of case reports*. World J. Biol. Psychiatry. 2009; 10(4 Pt 3): 944–952.
32. Fitzgerald M. *Schizophrenia and autism/Asperger's syndrome: Overlap and difference*. Clin. Neuropsychiatry. 2012; 9(4): 171–176.
33. Ghaziuddin M, Greden J. *Depression in children with autism/pervasive developmental disorders: A case-control family history study*. J. Autism Dev. Disord. 1998; 28(2): 111–115.
34. Loveland KA, Pearson DA, Tunali-Kotoski B, Ortegon J, Gibbs MC. *Judgments of social appropriateness by children and adolescents with autism*. J. Autism Dev. Disord. 2001; 31(4): 367–376.
35. Ghaziuddin M, Ghaziuddin N, Greden J. *Depression in persons with autism: Implications for research and clinical care*. J. Autism Dev. Disord. 2002; 32(4): 299–306.
36. Magnuson KM, Constantino JN. *Characterization of depression in children with autism spectrum disorders*. J. Dev. Behav. Pediatr. 2011; 32(4): 332–340.
37. Tantam D, Girgis S. *Recognition and treatment of Asperger syndrome in the community*. Br. Med. Bull. 2009; 89(1): 41–62.
38. Rao U, Chen LA. *Characteristics, correlates, and outcomes of childhood and adolescent depressive disorders*. Dialogues Clin. Neurosci. 2009; 11(1): 45–62.
39. Naidu A, James I, Mukaetova-Ladinska E, Briel R. *Diagnosis of Asperger syndrome in a 66-year old male presenting with depression*. Int. Psychogeriatr. 2006; 18(1): 171–173.
40. Spencer L, Lyketsos CG, Samstad E, Dokey A, Rostov D, Chisolm MS. *A suicidal adult in crisis: An unexpected diagnosis of autism spectrum disorder*. Am. J. Psychiatry. 2011; 168(9): 890–892.
41. Hellings J. *Psychopharmacology of mood disorders in persons with mental retardation and autism*. Dev. Disabil. Res. Rev. 1999; 5(4): 270–273.
42. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic Criteria for research*. WHO; 1992.
43. DeLong GR, Aldershof AL. *Long-term experience with lithium treatment in childhood: Correlation with clinical diagnosis*. J. Am. Acad. Child Adolesc. Psychiatry 1987; 26(3): 389–394.
44. 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(6): 932–935.
45. Kerbeshian J, Burd L, Fisher W. *Lithium carbonate in the treatment of two patients with infantile autism and atypical bipolar symptomatology*. J. Clin. Psychopharmacol. 1987; 7(6): 401–405.
46. Shafey H. *Use of lithium and flupenthixol in a patient with pervasive developmental disorder*. Am. J. Psychiatry. 1986; 143(5): 681.
47. Siegel M, Beresford C, Bunker M, Verdi M, Vishnevetsky D, Karlsson C et al. *Preliminary investigation of lithium for mood disorder symptoms in children and adolescents with autism spectrum disorder*. J. Child Adolesc. Psychopharmacol. 2014; 24(7): 399–402.
48. Sovner R. *The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders*. J. Clin. Psychiatry. 1989; 50(Suppl): 40–43.
49. Hollander E, Dolgoff-Kaspar R, Cartwright C, Rawitt R, Novotny S. *An open trial of divalproex sodium in autism spectrum disorders*. J. Clin. Psychiatry. 2001; 62(7): 530–534.

50. Komoto J, Usui S, Hirata J. *Infantile autism and affective disorder*. J. Autism Dev. Disord. 1984; 14(1): 81–84.

51. Joshi G, Biederman J, Wozniak J, Doyle R, Hammerness P, Galdo M et al. *Response to second generation antipsychotics in youth with comorbid bipolar disorder and autism spectrum disorder*. CNS Neurosci. Ther. 2012; 18(1): 28–33.

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