Comparison of Symptoms of Pediatric Bipolar Disorder in the Manic Phase and Attention Deficit and Hyperactivity Disorder

Mehmet Fatih Ceylan¹, Omer Faruk Akca², Murat Yuce³, Sahin Bodur¹

ÖZET

Pediatrik bipolar bozukluk manik dönem belirtilerinin dikkat eksikliği ve hiperaktivite bozukluğu belirtileri ile karşılaştırılması

Amaç: Erişkin bipolar bozukluğu çoğunlukla epizodik seyir göstermektedir. Ancak pediatrik bipolar bozuklukta karma epizodlar ve hızlı döngü erişkin bipolar bozukluğa göre daha sık görülen durumlardır ve beraberinde Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB) tanısı sıklıkla bulunmaktadır. Bu çalışmanın amacı pediatrik bipolar bozukluk tanısı almış bir grup hastada bu bozukluğun klinik karakteristik özelliklerini belirlemek ve bu özellikleri DEHB tanısı olan hastalar ile karşılaştırmaktır.

Yöntem: Örneklem DSM-IV tanı kritelerine göre pediatrik bipolar bozukluk manik dönem ve DEHB tanıları konulmuş olan 19'ar çocuk veya ergen hastadan oluşmaktadır. Hastalığın başlama yaşı, belirtiler ve eş tanılar analiz edilmiştir. Daha sonra iki grup Child Mania Rating Scale ile belirlenmiş olan hastalık belirtileri bakımından karşılaştırılmıştır.

Bulgular: İrritabl duygudurum (%94), hızlı duygudurum dalgalanmaları (%89), sanrılar (%94), işitsel (%63) ve görsel hallusinasyonlar (%43) bipolar bozukluğu olan hastalarda istatistiksel olarak anlamlı olarak daha sık saptanmıştır. Hareketlilik, dikkat eksikliği ve irritabilite oranları bakımından her iki grup arasında anlamlı fark bulunmamıştır.

Sonuç: Bipolar bozukluğu olan çocuk ve ergenlerde hızlı döngü, irritabl duygudurum ve psikotik belirtiler sık olarak görülmektedir ancak irritabilite bipolar bozukluk için spesifik bir semptom değildir.

Anahtar sözcükler: Pediatrik bipolar bozukluk, duygudurum, irritabilite, psikotik belirtiler, dikkat eksikliği ve hiperaktivite bozukluğu

Klinik Psikofarmakoloji Bülteni 2012;22(2):161-6

ABSTRACT:

Comparison of symptoms of pediatric bipolar disorder in the manic phase and attention deficit and hyperactivity disorder

Objectives: The clinical presentation of Bipolar Disorder (BD) in adults often has an episodic course. However, pediatric onset BD often presents with higher rates of mixed episodes, rapid cycling, and co-occurring Attention-Deficit/Hyperactivity Disorder (ADHD) than adults with BD. The aim of this study is to describe the clinical characteristics of pediatric onset BD in a Turkish sample and to compare these characteristics with children with a diagnosis of Attention Deficit and Hyperactivity Disorder (ADHD).

Methods: A total of 19 child or adolescent patients diagnosed with BD in the manic state and 19 child or adolescent patients diagnosed with ADHD based on DSM-IV criteria were included in the study. The children were analyzed in terms of age of onset, symptoms, and comorbidity. Subsequently, both groups were compared in terms of symptoms of BD according to the Child Mania Rating Scale.

Results: Irritable mood (94%), rapid mood swings (89%), delusions (94%), auditory (63%) and visual hallucinations (47%) were detected statistically more commonly in the bipolar disorder patients. There were no significant differences between the two groups in terms of hyperactivity, distractibility, and irritability.

Conclusion: Children and adolescents with BD often present with higher rates of rapid mood swings, irritable mood, and psychotic features. However, irritability does not seem to be a specific symptom for pediatric BD.

Key words: Pediatric bipolar disorder, mood, irritability, psychotic signs, attention-deficit/hyperactivity disorder

Bulletin of Clinical Psychopharmacology 2012;22(2):161-6

¹M.D., Dr. Sami Ulus Çocuk Hastanesi Eğitim ve Araştırma Hastanesi Çocuk ve Ergen Psikiyatrisi Kliniği, Ankara - Turkey ²M.D., Samsun Ruh Sağlığı ve Hastalıkları Hastanesi Çocuk ve Ergen Psikiyatrisi Kliniği, Samsun - Turkey ³M.D., Ondokuz Mayıs Üniversitesi Çocuk ve Ergen Psikiyatrisi AD., Samsun - Turkey

Yazışma Adresi / Address reprint requests to: Mehmet Fatih Ceylan, Dr. Sami Ulus Çocuk Hastanesi Eğitim ve Araştırma Hastanesi Çocuk ve Ergen Psikiyatrisi Kliniği, Ankara - Turkey

Elektronik posta adresi / E-mail address: mehmetfceylan@yahoo.com

Gönderme tarihi / Date of submission: 1 Ocak 2012 / January 1, 2012

Kabul tarihi / Date of acceptance: 12 Nisan 2012 / April 12, 2012

Bağıntı beyanı:

M.F.C., O.F.A., M.Y., S.B.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

${\bf Declaration\ of\ interest:}$

M.F.C., O.F.A., M.Y., S.B.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Bipolar disorder (BD) is a common psychiatric disorder that is associated with significant morbidity and mortality. It is most frequently diagnosed between the ages of 18 and 24, but as many as 59% of adult patients with BD experience their first episode before the age of 18 (1). Child and adolescent onset of bipolar disorder is a relatively new concept which has not been studied as much as adult BD (2). In the past decade, there has been a proliferation in the number of children and adolescents diagnosed with BD. Pediatric Bipolar Disorder (PBD) often presents with higher rates of mixed episodes, rapid cycling, and co-occurring Attention-Deficit/Hyperactivity Disorder (ADHD) than adults with BD. The clinical presentation of BD in adults often has an episodic course, with individuals switching from distinct affective episodes of depression, mania or hypomania, and euthymia. In children, however, agreement on the clinical presentation of BD is less clear, with some studies indicating a more chronic course of symptoms with a more irritable and violent presentation during manic states (3,4). Biederman and colleagues emphasized in their case series that children with BD have irritability rather than euphoria, and that the severity of the irritability in PBD differentiates it from other illnesses. They have found that only 33% of children had euphoria, while 92% had irritability in the manic state (5).

Although the frequency of childhood and adolescent BD is stated to be 1% in the normal population (6), children and adolescents in Turkey are diagnosed less frequently with BD. Research studies suggest that PBD may not be rare but that it may be difficult to diagnose (7). These children may be diagnosed with other psychiatric disorders which have similar symptoms to BD (e.g. disruptive behavior disorders —especially ADHD- and psychotic disorders). These disorders will be elucidated as differential diagnoses of BD in the Discussion section of this paper.

Our aim within this study is to compare the symptoms of bipolar disorder in the manic phase and ADHD in Turkish children and adolescents, to describe the main features of BD in children and adolescents and to determine the differences between child-adolescent BD and ADHD in a Turkish population (8-10). This is the first study which has used the Child Mania Rating Scale, Parent Version (CMRS-P) in a Turkish population.

METHOD

Subjects

The PBD group included 19 patients admitted to Gaziantep University Child and Adolescent Psychiatry Department with a diagnosis of BD in the manic state between the years of 2006 and 2008. Sixteen of them were hospitalised and the others were followed on an outpatient basis. The ADHD group consisted of 19 patients who were treated at Dr. Sami Ulus Hospital Child and Adolescent Psychiatry outpatient clinic between May 2011 and November 2011 with a diagnosis of ADHD. The age and gender of the two groups were homogenious, and there were no significant differences between the groups. The psychiatric diagnoses were made by a child and adolescent psychiatrist according to DSM-IV criteria and all subjects were screened for psychiatric disorders according to the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL).

Procedure

All patients in both groups received The Child Mania Rating Scale, Parent Version (CMRS-P) before a treatment was given. All participants and their parents were informed about the study and informed consent was obtained from parents. The sociodemographic information records of the patients were reviewed by the researchers. Severe symptomatic PBD patients were hospitalized and the others were followed at an outpatient clinic.

MATERIALS

K-SADS-PL

K-SADS-PL is a semi-structured interview used to identify current and lifetime psychopathology in children and adolescents (11). Mood disorders, psychotic disorders, anxiety disorders, eliminating disorders, disruptive behavior disorders, substance abuse, eating disorders, and tic disorders can be assessed with K-SADS-PL. A Turkish adaptation of this form was made by Gökler and colleagues (12). KSADS-PL was administered to all patients while taking the DSM-IV criteria into consideration (13).

Child Mania Rating Scale, Parent Version (CMRS-P)

The CMRS-P is the first parent reporting measure developed specifically to assess child and adolescent mania. Internal consistency and retest reliability suggest that the CMRS-P is a reliable and valid instrument (14). It includes 21 items reflecting the DSM-IV criteria for a manic episode (13). Each item is answered on a four-point Likert type scale anchored by 0 (Never/Rare), 1 (Sometimes), 2 (Often), and 3 (Very Often). Parents are instructed to check "never" or "rare" if the behavior is not causing trouble. In the present study, the measure was completed by the mothers (89%) or fathers (11%) of the children.

Data Analysis

Differences between groups were analyzed using the Mann Whitney U test for continuous variables and the Chi Square or Fischer tests for categorical variables. In the evaluation of manic symptoms by the CMRS-P, the zero and 1 points were assumed to be negative and the 2 and 3 points were assumed to be positive. Descriptive analyses were also performed. Differences were accepted as significant when p< 0.05.

RESULTS

The population consisted of 19 child or adolescent patients diagnosed with bipolar disorder. Eighteen of the patients were diagnosed as early onset (adolescent onset) and one was diagnosed as very early onset (child onset) BD (age<13). The mean age of the patients was 15.3 and 7 of the 19 patients were female. The age and gender of the patients in both groups was homogenious and there were no significant differences between the groups (p> 0.05). The demographic data and comorbidities for the subjects are summarised in Table 1.

With respect to ADHD subtype, 57% (n=11) of the patients were diagnosed with ADHD-combined type, 37% (n=7) were diagnosed with ADHD-inattentive type, and 5% (n=1) of the patients were diagnosed with ADHD-

Table 1: Demographics and comorbidity				
Variables	PBD	ADHD	р	
Sex: Male/Female (n)	12/7	13/6	p=0,73	
Age: mean (year)	15,3	14,7	p=0,15	
Age: range (year)	9-17	10-17		
Comorbid Disorders				
ADHD	63% (n=12)	100% (n=19)		
ODD	63% (n=12)	52% (n=10)	p=0.51	
Anxiety Disorders	37% (n=7)	42% (n=8)	p=1,00	

PBD: Pediatric Bipolar Disorder, ADHD: Attention Deficit/Hyperactivity Disorder, ODD: Oppositional Defiant Disorder

Symptom	PBD n (%)	ADHD n (%)	χ^2	р
Elated mood	13(68)	3(15)	10,7	*0,001
Irritable mood	18(94)	15(78)	F	0,34
Grandiosity	11(57)	1(5)	12,1	*<0,001
Delusional grandiosity	6(31)	0(0)	F	*0,02
Decreased need for sleep	13(68)	8(42)	2,6	0,103
Too much energy	17(89)	18(94)	F	1.00
Pressured speech	17(89)	12(63)	F	0,124
Racing thoughts	16(84)	4(21)	15,2	*<0,001
Flight of ideas	17(89)	8(42)	9,4	*0,002
Hyperactivity	15(78)	17(89)	F	0,66
Distractibility	19(100)	18(94)	F	1.00
Overproductive	9(47)	0(0)	F	*0,001
Hypersexuality	13(68)	2(10)	13,3	*<0,001
Disinhibited	15(78)	8(42)	5,3	*0,02
Poor judgment	12(63)	5(26)	5,2	*0,02
Rage attacks	16(84)	15(78)	F	1.00
Overly jocular	11(78)	8(42)	0,9	0,33
Rapid mood swings	17(89)	6(31)	13,3	*<0,001
Delusions	18(94)	0(0)	34,2	*<0,001
Auditory hallucinations	12(63)	0(0)	17,5	*<0,001
Visual hallucinations	9(47)	0(0)	F	*0,001
F=Fischer				
χ ² =Chi square				

hyperactive/impulsive type.

Irritable mood (94%), rapid mood swings (89%), delusions (94%), auditory (63%) and visual hallucinations (47%) were detected commonly in the patients with bipolar disorder. Although some differences occurred in terms of symptoms, there were no significant differences between the two groups in terms of hyperactivity, distractibility, and irritability. The main clinical features of the patients are presented in Table 2.

Eighty four percent (n=16) of the patients with BD were hospitalised and the others were followed at an outpatient clinic.

DISCUSSION

PBD is a serious illness that can lead to higher suicide rates, problems in school, aggression, and high-risk behaviors such as sexual promiscuity and substance abuse (15,16). It is characterized by high relapse rates and low rates of recovery (4,17,18). There is a consensus among researchers and clinicians about the difficulty of diagnosing pediatric mania. This difficulty is primarily due to the clinical presentation of mania in children and the overlapping of symptoms of mania with ADHD. PBD phenomenology is often mixed and dysphoria with 'affective storms' and severe outbursts of anger are much more frequent than euphoria. The course is often chronic, discontinuous, and erratic (3,16).

One of the main findings of this study is that many of the patients with PBD were also having psychotic symptoms. Manic symptoms of adolescents with PBD are usually complicated; psychotic symptoms and mixed depressive and manic symptoms can be seen during these episodes. Psychotic features associated with pediatriconset mania include auditory hallucinations, persecutory delusions, passive feelings of mind control, and cognitive disorganization with loosening of associations and incoherence (19). For many years, children and adolescents who exhibited severe mood swings and highly erratic behavior were likely to be diagnosed as a psychotic disorder, such as schizophrenia (20). But, in recent years, systematic research studies have shown a dramatic increase in the number of children and adolescents being diagnosed with bipolar disorder. According to some authors; as many as 50% of early-onset bipolar disorder cases are misdiagnosed as schizophrenia (20-22). Our study supports

the view that children who present with psychotic symptoms should not be diagnosed as psychotic disorder hastily.

Distractibility, disinhibition, and hyperactivity signs were commonly observed in both groups of this study and these signs appeared not to be specific to PBD or ADHD. There were no significant differences between two groups in terms of these symptoms. In addition, comorbidity of ADHD is common in children and adolescents with BD. Studies indicate that as many as 60 to 90% of youth with PBD have comorbid ADHD (23). Consistent with this knowledge, 63% of the patients in the PBD group of this study presented with comorbid ADHD. Therefore, the differential diagnosis or comorbidity of these two disorders is very important. Many of the symptoms of PBD (e.g., affective instability, aggression) were once considered to be symptoms associated with ADHD. But, Carlson (1998) speculated that those who do not fit the more restricted diagnostic criteria for ADHD are being diagnosed with bipolar disorder because a single diagnosis of ADHD fails to adequately capture the breadth of their problems (17). In the literature, a more episodic presentation of symptoms is stated to be suggestive of a mood disorder and a more chronically persistent presentation suggests ADHD. Likewise, rapid mood swings were more frequent in PBD in our study. Chronic hyperactivity, impulsiveness, and attention problems with episodic exacerbation would be consistent with comorbid PBD superimposed on ADHD (24).

Rapid mood swings (89%) and irritability (94%) symptoms were frequent in both groups. However, there was no significant difference in terms of irritability between the two groups. Geller found, using specific definitions of cycling, that of 60 bipolar patients (aged 7–16 years old) 83% showed some form of rapid cycling with 8% classified as 'ultra-rapid' (episodes lasting a few days to a few weeks) and 75% classified as 'ultradian' (variation occurring within a 24-hour period) (25). Irritability is one of the main moods and characterized by the emotion of anger and temper outbursts. Irritability is not assumed to be a specific symptom of BD. It is also seen in depression, anxiety and ADHD (13). However, the irritability of PBD patients ("super angry, grouchy, or cranky") is stated to be more serious than the irritability of other disorders. Additionally, in comparison with other disorders, the irritability seen in PBD causes more serious

There are some limitations of this study such as the

sample size of the study was small and the PBD patients

and the ADHD patients were enrolled from different

centers at different times. Additionally, the reliability and

validity of the CMRS-P was not determined on a Turkish

In conclusion, there has been an increase in the

impairments in functionality (5,26). In addition, decreased sleep and inappropriate sexual behavior more frequently accompany the irritability seen in PBD in comparison with other disorders (27). Although irritability is mostly episodic in adult BD, chronic irritability is more frequent in PBD. Some investigators have suggested that overlapping symptoms like irritability are not of diagnostic importance as they failed to differentiate ADHD and BD in one study, and suggest that elated mood and grandiosity are of greater diagnostic importance to BD than is irritability (15). Similarly, in our study, elated mood and grandiosity were significantly more frequent in PBD children.

Proper assessment of PBD is essential in early diagnosis and intervention. Evidence has shown that although symptoms may appear very early in childhood, there is an average delay of diagnosis estimated to be around seven years (28). Early intervention could lead to a better prognosis. However, very little information on early intervention is available in the PBD literature.

prognosis typhough che is an timeseven see

population.

knowledge about PBD.

diagnosis of PBD in recent years. In the US, the rates of diagnosis of BD in children and adolescents have shown an increase of about 500% over the last decade (29). One reason for this dramatic increase may have been the result of the assertion that irritability, which is continually present from a very young age, should be considered the typical mood of early mania (30). Mick et al. reported that children with very severe forms of irritability were several times more likely to suffer from BD (31). Adolescents with serious mood swings, irritability, elated mood and

psychotic symptoms usually are evaluated in terms of BD.

Studies with larger samples are necessary to increase our

References:

- Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994; 31(4):281-94.
- Sanchez L, Hagino O, Weller, E, Weller R. Bipolarity in Children. Psychiatr Clin North Am 1999; 22(3):629-48.
- Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 1995; 34(7):867-76.
- Geller B, Tillman R, Craney JL, Bolhofner K. Fouryear prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 2004; 61(5):459-67.
- Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Cayton GA, et al. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. J Psychiatr Res 2005; 39(6):611-22.
- Pataki CS. Mood disorders and suicide in children and adolescents. In Comprehensive Textbook of Psychiatry, Sadock BJ, Freedman AM, Kaplan HI (editors). 7th ed. Philadelphia: Williams and Wilkins; 2000. p. 2740-67.
- Biederman J, Mick E, Faraone SV, Spencer T, Wilens TE, Wozniak J. Current concepts in the validity, diagnosis and treatment of paediatric bipolar disorder. Int J Neuropsychopharmacol 2003; 6(3):293-300.

- Diler RS, Uguz S, Seydaoglu G, Avcı A. Mania profile in a community sample of prepubertal children in Turkey. Bipolar Disord 2008; 10(4):546-53.
- Inal-Emiroglu FN, Baykara B, Miral S. A case series of Turkish children and adolescents with bipolar spectrum disorder: a naturalistic clinical phenomenological follow-up. Minerva Pediatr 2008; 60(1):51-7.
- Diler RS, Uguz S, Seydaoglu, Erol N, Avcı A. Differentiating bipolar disorder in Turkish prepubertal children with attentiondeficit hyperactivity disorder. Bipolar Disord 2007; 9(3):243-51.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36(7):980-8.
- 12. Gökler B, Ünal F, Pehlivantürk B, Kültür EÇ, Akdemir D, Taner Y. Okul çağı çocukları için duygulanım bozuklukları ve şizofreni görüşma çizelgesi-şimdi ve yaşamboyu şekli- Türkçe uyarlanmasının geçerlilik ve güvenirliği. Çocuk ve Gençlik Ruh Sağlığı Dergisi 2004; 11(3):109-16 (Turkish).
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder. 4th ed. Washington DC: American Psychiatric Association; 1994.
- Pavuluri MN, Henry DB, Devineni B, Carbray JA, Birmaher B. Child mania rating scale: development, reliability, and validity. J Am Acad Child Adolesc Psychiatry 2006; 45(5):550-60.

- Geller B, Zimerman B, Williams M, Delbello MP, Bolhofner K, Craney JL, et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002; 12(1):11-25.
- Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 2005; 44(9):846-71.
- Carlson GA, Kelly KL. Manic symptoms in psychiatrically hospitalized children--what do they mean? J Affect Disord 1998; 51(2):123-35.
- 18. Chang KD. Course and impact of bipolar disorder in young patients. J Clin Psychiatry 2010; 71(2): e05.
- Faedda GL, Baldessarini RJ, Suppes T, Tondo L, Becker I, Lipschitz D. Pediatric-onset bipolar disorder: a neglected clinical and public health problem. Harv Rev Psychiatry 1995; 3(4):171-95.
- Carlson GA. Child and adolescent mania--diagnostic considerations. J Child Psychol Psychiatry 1990; 31(3):331-41.
- Werry JS, McClellan JM, Chard L. Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: a clinical and outcome study. J Am Acad Child Adolesc Psychiatry 1991; 30(3):457-65.
- McClellan JM, Werry JS, Ham M. A follow-up study of early onset psychosis: comparison between outcome diagnoses of schizophrenia, mood disorders, and personality disorders. J Autism Dev Disord 1993; 23(2):243-62.
- Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006; 63(10):1139-48.

- Youngstrom EA, Birmaher B, Findling RL. Pediatric bipolar disorder: validity, phenomenology, and recommendations for diagnosis. Bipolar Disord 2008; 10(1):194-214.
- Geller B. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. J Affect Disord 1998; 51(2):81-91.
- Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry 2006; 60(9):991-7.
- Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. Am J Psychiatry 2003; 160(3):430-7.
- Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB. Pediatric bipolar disorder: phenomenology and course of illness. Bipolar Disord 2004; 6(4):305-13.
- Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996–2004. Biol Psychiatry 2007; 62(2):107-14.
- Leibenluft E, Cohen P, Gorrindo T Brook JS, Pine DS. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. J Child Adolesc Psychopharmacol 2006;16(4):456-66.
- Mick E, Spencer T, Wozniak J, Biederman J. Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. Biol Psychiatry 2005; 58(7):576-82.