ATOMOXETINE IN THE TREATMENT OF THE MOST COMMON COMORBID DISORDERS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, OPPOSITIONAL DEFIANT DISORDER AND ANXIETY DISORDERS

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) in childhood or adolescence is associated with a significantly higher lifetime risk of oppositional defiant disorder, anxiety disorder, conduct disorder, among others. Reports of co-morbidity rates are variable and influenced by assesment methodology and refferal bias, and may reflect lifetime rates within clinical groups. Up-to date studies revealed that as many as 85% of patients with ADHD have at least one psychiatric comorbidity and approximately 60% have at least two. Research and clinical practice has shown that having multiple co-existing psychiatric problems increase the severity of ADHD and behavioural problems, and is associated with incereased psychosocial impairment. The high rate of psychiatric problems co-occuring with ADHD has strong implications for the management of these patients. The presence of co-existing psychiatric conditions may moderate the response to treatment of ADHD and ADHD treatments may adversely affect and exacerbate the symptoms of the co-morbit condition.

The aim of this article was to summarize the use of atomoxetine in the most frequent co-morbid disorders accompaining ADHD, ODD (oppositional defiant disorder) and anxiety, and to emphazise decrease of co-morbid symptoms with treatment of atomoxetine what exhort us to think about them as about possible subtypes of ADHD.

Key words: ADHD, comorbidity, ODD, anxiety, atomoxetine

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a central nervous system disorder that has an onset in childhood and has been estimated to occur in 3 to 7% of school-aged children around the world [1]. According to ICD-10, to diagnose ADHD, symptoms of hyperactivity, impulsivity and inattention are needed. Disorder typically begins in pre-school age of children and have chronical course.

Children with ADHD often present with behavioral problems, impaired academic performance, and decreased social functioning [2]. Longitudinal studies have demostrated,that while there is a clear reduction and modification in symptoms with age, ADHD can persist into adulthood with estimated persistance rates of 15% for full ADHD diagnosis [3]. ADHD was taken as a mythus for a long time, with denies of its biological base. Only psychosocial context was accepeted as a trigger of disease. In the 20th century, with extension of scientific approaches into psychiatry, neurophysiological, structural, biochemical and genetic diferences were discovered between ADHD patients and healthy controls [4].

ADHD can be considered as a disorder of neurotransmitter function, with particular focus on decrease of the neurotransmitters dopamine and norepinephrine. There has been extensive research conducted that demonstrates that dopamine is critical in the regulation of learning, as well as maintaining trained or conditioned responses and motivated (goal-directed) behaviors [5]. Dopamine also plays an important role in working memory, the abil-

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ity to „keep something in mind“ for a brief period of time [6]. Thus, dopamine can modulate neuronal activity related to motor activity that is guided by external cues and is goal directed [7]. Dopamine plays an important role in the function of the prefrontal-subcortical system. Norepinephrine (noradrenaline) is involved in maintaining alertness and attention. Norepinephrine neurons are triggered by novel and important stimuli and are quiescent during sleep [8].

According to the neurobiological findings, as etiology of ADHD, the only efficient therapy is medicamentous. Several studies confirmed efficiacy of medicamentous therapy itself or in combination with behavioral approaches as superior to behavioral treatment alone or community care [9].

Nowadays, there are two registrated drugs as a specific treatment for ADHD in Slovakia. Atomoxetine and metylphenidate in new formulation-OROS form. The osmotic-controlled release oral delivery system, OROS, is an advanced drug delivery technology that uses osmotic pressure as the driving force to deliver pharmacotherapy, usually once-daily, in several therapeutic areas. Drug delivery using the various OROS products can result in an improved safety profile, stable drug concentrations, uniform drug effects, and reduced dosing frequency. OROS technology has also enabled the use of an effective starting dose, without the need for dose titration, which allows the achievement of symptom control much earlier than that observed with immediate-release preparations. Such attributes can enhance patient compliance and convenience, thereby ensuring efficacy and improving patient outcomes [10].

Atomoxetine is a selective norepinephrine reuptake inhibitor, indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults. Atomoxetine affects the regulation of norepinephrine by acting as a potent and highly specific inhibitor of the presynaptic norepinephrine transporter. Atomoxetine has minimal affinity for other transporter or receptor systems.

Metylphenidate is a stimulant of central nervous system, which probably inhibits reuptake of dopamine in brain [11]. Therapheutic role of metyfenidat s effect on noradrenergic system is discussed in several studies [12].

Nonstimulant agents, such as atomoxetine (FDA-approved), and several non-approved agents, bupropion, guanfacine and clonidine, may offer necessary alternatives to the stimulants [13]. This is especially important for patients who have comorbidities that are contraindicated for stimulant use based on medical issues and/or risk for stimulant abuse. Approximately 10–30% of patients either do not respond to or must avoid stimulant therapy [13].

Pharmacologic properties of atomoxetine

Atomoxetine is a (-) isomer of an ortho-methylphenoxy analogue of nisoxetine, and is a derivate of phenoxypropylamine [14]. Its mechanism of action in the treatment is related to its selective inhibition of presynaptic norephinephrine reuptake in the prefrontal cortex, resulting in increased noradrenergic transmission, important for attention, learning, memory and adaptive response [15]. Atomoxetine has a high affinity and selectivity for norephnephrine transporters.

When norephinephrine and serotonine depletion was induced in the rat brain in vivo, using the transporter – specific neurotoxins, atomoxetine was shown to inhibit the depletion of norephinephrine, but not serotonin, in a dose-depent manner [16]. Localization studies, using quantitative autoradiography in the rat brain, suggest that atomoxetine preferentially binds to areas of known high distribution of naoradrenergic neurons, such as fronto-subcortical system, which controls attention and motor behaviour [17].

In rats, intraperitoneal atomoxetine significantly ($p < 0.025$) increased extracellular norepinephrine and dopamine levels in the prefrontal cortex. Extracellular dopamine levels in the nucleus accumbens and striatum remained constant, what suggests that atomoxetine is unlikely to produce tics or have abuse potential [16].

Atomoxetine was associatd with modest increases in heart rate and BP in children and adolescents with ADHD, according to the pooled analysis of clinical trial data [18].

In the short term study (up to 9 week's therapy), significantly greater increases in mean heart rate and mean diastolic BP were seen with atomoxetine than with place; there were no significant between - group difference in the change in systolic BP. Patients recieving atomoxetine for ≥1year had increases in mean heart rate of < 10 bpm and mean increases in BP that were small and considered to be of clinical significance [18].

Atomoxetine recipients demonstrated an initial loss in both expected weight and height, althought these shortfalls peaked at 15 and 18 month, respectively, and returned to expected measurements by 36 and 24 month [19]. Persistent decrease from the expected measurements appeared to occur in patients who were taller or heavier than avarage before treatment [19].

Atomoxetine appears less likely than methylphenidate to exacerbate disordered sleep in pediatric patients with ADHD [20].

Oral atomoxetine is rapidly absorbed; Cmax is reached in 2 hours among children and adolescents with ADHD [21]. Studies demonstrated an absolute oral bioavailability of 63% in extensive metabolizers and 94% in poor metabolizers [22]. Atomoxetine demonstrates dose-proportional increases in plasma exposure, slightly affected by administration with food. Plasma protein binding (mainly to albumin) of atomoxetine was 98% at therapeutic concentration [22].

Atomoxetine undergoes extensive biotransformation, mainly via the CYP2D4 enzymatic pathway in which atomoxetine is oxidated to form 4-hydroxyatomoxetine (the major metabolite), which is then glucuronidated to form 4-hydroxyatomoxetine-O-glucuronide, the main execreted. Poor metabolizers are unable to metabolize as efficiently using the CYP2D6 pathway; metabolism in these individuals occurs mainly via CYP2C19 pathway, forming N-desmethoxyatomoxetine. 4-Hydroxyatomoxetine has similar pharmacologic activity to atomoxetine, N-desmethoxyatomoxetine has much less pharmacologic activity than atomoxetine and 4-Hydroxyatomoxetine. Extensive metabolizers with moderate (Child-Pugh clss B) or severe (Child-Pugh class C) hepatic insufificiency have increased atomoxetine exposure compared with voluntares [22]. In extensive metabolizers is a half-life of atomoxetine 5.2 hours [23] in compare with slow metabolizers, in which atomoxetine is metabolized through several alternative CYP pathways, that last 22 hours

The effectiveness and safety of atomoxetine in treating ADHD in children and adolescents were originally established in several short-term studies and some long-term studies, preferably aimed on core symptoms. Only few studies have prospectively addressed the effect of nonstimulant treatment with ATX on comorbidity disorder (note: comorbidity means coexistence of at least 2 mental disorders in one patient at the same time), and with conflicting results. The same little number of studies was focused on effectivness of ATX on core symptoms of ADHD with comorbidity. Next systematic and detailed research in this area is needed mostly for clinical practice.

Atomoxetine improved ADHD symptoms compared to placebo as rated by statistically significant improvements versus placebo in the total score of the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS). An investigator administered the ADHD-RS to the parent and/or teacher and clinical investigation of psychiatrists, depending on the study design. Symptom improvement was also observed using secondary measures, and these results demonstrate the efficacy of atomoxetine in children and adolescents in both home and school settings. Atomoxetine improved symptoms equally well in the inattentive and hyperactive/impulsive domains [25]. The response to treatment was dose-dependent, with an optimal dose of approximately 1.2 mg/kg/day and no additional improvement in group-results of core symptoms at 1.8 mg/kg/day. The full effect of therapy is seen in 6-8 weeks. Atomoxetine is efficacious when dosed once daily in the morning, or as a divided dose in the morning and early evening.

Co-existing disorders with ADHD pervasively affect research and clinical practice as a result of its influence on diagnosis, prognosis and treatment. Patients with ADHD having comorbidity were usually excluded from studies, so despite the thousands of scientific articles, little is known about effect of atomoxetine on comorbidity in ADHD (ODD, anxiety). And that is the reason, why next research would be contributive.

The efficacy of atomoxetine in treating core symptoms of ADHD seems to be unaffected by the presence of co-morbid conditions so far. The tolerability profile of atomoxetine in patients with ADHD and comorbid conditions was similar to that of patients with uncomplicated ADHD. Atomoxetine was well tolerated, with adverse events generally mild and transient; the most frequent adverse events in patients with ADHD include abdominal pain, decreased appetite, nausea and vomiting.

Oppositional defiant disorder

Oppositional defiant disorder (ODD), one of the conduct disorders, is the most common comorbid condition associated with ADHD, occurring in 30 to 60% of children with ADHD [15, 26]. ODD is characterized by a pattern of developmentally inappropriate negativistic, hostile, and defiant behaviors causing clinically significant impairment in social, family, or academic functioning. Children and adolescents with ADHD and comorbid ODD tend to present with more severe ADHD symptoms, peer problems, and family distress, which in turn are associated with increased severity of the disorder and a poorer prognosis [27].

The etiology of conduct disorder involves an interaction of genetic/constitutional, biological and psychosocial factors. Children who have conduct disorder may inherit decreased baseline autonomic nervous system activity, requiring greater stimulation to achieve optimal arousal [28].

This hereditary factor may account for the high level of sensation-seeking activity associated with conduct disorder [29].

Current research focuses on defining neurotransmitters that play a role in aggression, with serotonin most strongly implicated [30]. Changes in testosteron and serotonine blood levels eventually decreased activity of dopamin – beta-hydroxylasis are common laboratory findings in children with ODD.

Because of the multifaceted nature of conduct problems, particularly related comorbidities, treatment usually includes medication, teaching parenting skills, family therapy, and consultation with the school. Studies have shown that youth with predatory and severe aggression are not likely to respond without medication and they have a better response to a multimodal approach [31]. Medications may help, however, when there are co-occurring disorders, making it more likely that the youth will be able to participate and benefit from intervention strategies. Pharmacological interventions may be helpful, for example, when a child or adolescent has a disorder that is responsive to medication, such as ADHD or bipolar disorder. Medications often prescribed for ADHD, such as stimulants and atomoxetine, may help improve oppositional behaviors as well. There is also limited research suggesting that mood stabilizers or selective serotonin reuptake inhibitors (SSRIs) may be helpful when there is a co-occurring mood disorder, such as bipolar or major depressive disorder. Atypical antipsychotics are the most commonly prescribed medication for aggression associated with ODD and CD. Medications should be started only after an appropriate baseline of symptoms or behaviors has been obtained and only in conjunction with psychosocial treatment [32].

Table 1 Pharmacotherapy ussually used in treating comorbid ODD

Medication	Dosage range	Mechanism of action	Common adverse effects	Monitoring/special considerations
Methyphenidate	0,3-0,6 mg/kg/day max 54 mg/day	Central nervous system stimulant Inhibition of dopamine reuptake	Anorexia, nervousness, sleep delay, restlessness, dysrhythmias, palpitations, tachycardia, anemia, leukopenia	Periodic CBC with differential and platelet count, blood pressure, height, weight, heart rate
Atomoxetine	After 6 year Starting dose 0.5 mg/kg/day to therapeutical dose 1.2 mg/kg/day	Selective reuptake inhibition of noradrenalin	Lack of appetite, wieght loss, nausea, increase of BP and HR	Regular control of CV parameters
Risperidone	Low doses ½-1 mg per day	Selective agonist of 5HT2 and D2 receptors	Extrapyramidal syndrome, somnolence, higher level of hyperprolakctinemia, getting on weight, orthostatic hypotension	
Lithium	First week 150-300 mg ped day, after 14 days increase by 300 mg/day	Several ways of effect: Effect on G-protein, second messangers, inhibition of adenylcyklasis and inositol-1-fosfatasis proteinkinasis C, agonist of S1A receptors, blockage of oversenzitivity in dopamin receptors	Enuresis, fatigue, ataxie, diplopia, dysatrie, cefalea, nauzea, tremor	Drug interactions Serum lithium concentrations prior to next dose, monitor biweekly until stable then every 2 to 3 months; serum creatinine, CBC, urinalysis, serum electrolyte, fasting glucose, echocardiogram, TSH
Carbamazepine	>7 years: Start with 100 mg in 2 doses, max 400-800 mg/day in 2-4 doses 6 to 12 years: 200 mg twice daily; increase by 100 mg at weekly intervals; maximum dosage of 1.000 mg per day	Influence on serotonergic system, agonist of GABA-B receptors, stabilization of Na+ an Ca+ membrane canals Specific affinity to limbic structures and inhibition of permeability reticulothalamic and thalamocorticalis circuits. Supress activity of efferent conections from thalamus and aferentation to hippocampus and decrease activity of connections between amygdala to thalamus and hippocampus to thalamus	Ataxia, drowsiness, constipation, diarrhea, nausea	CBC with platelet count, liver function tests
Valproic acids	10 to 15 mg per kg per day in 1 to 3 divided doses; increase by 5 to 10 mg per kg per day at weekly intervals Max 500-2000 mg day		Drowsiness, sedation, constipation, diarrhea, heartburn, nausea, vomiting, rash	Liver function tests, bilirubin, CBC with platelet count
Bupropion	3 mg/kg/day, 3x day, max 400 mg/day	Inhibition of noradrenaline and dopamin reuptake	Agitation, anxiety, confusion, headache/migraine, insomnia, seizures, arrhythmias, nausea, vomiting	

Clonidine	0.05 mg per day; increase every 3 to 7 days by 0.05 mg per day to 3 to 5 g per kg per day in 3 to 4 divided doses Maximum dose: 0.3 to 0.4 mg per day		Dizziness, drowsiness, sedation, constipation, dry mouth	Blood pressure, heart rate Do not discontinue abruptly or withdrawal symptoms may occur.
Trazodone	4.8+/- 1.7 mg/kg/day	presynaptic selective reuptake inhibition of 5-HT receptors	Orthostatic hypotension, drowsiness, fatigue, irritability, painfull erection	
Tiaprid	50-200 mg per day	Selective inhibition of D2 and D3 receptors	Fatigue, insomnia, agitation, vertigo, cefalea	Prolactinemia blood levels controls

CBC- complete blood count, **CV**- cardiovascular, **HR**- heart rate, **HT**- 5-hydroxytryptamine receptors, **D**-dopamine receptors, **S**-serotonine receptors, **TSH**- Thyroid-stimulating hormone

The co-occurrence of ADHD and ODD symptoms is greater than might be expected from chance, raising the possibility that some association exists between the two sets of symptoms [33] and indeed it has been suggested that greater severity, at least in the hyperactivity/impulsivity dimension of ADHD symptoms, may predict the later development of oppositional symptoms [34]. Moreover, these externalizing disorders may share some common genetic underpinnings, as genetic variation in both dopaminergic [35] and androgenic receptors [36] appears to play a role in their expression. On the other hand, factor analysis points to the independence of the inattentive, hyperactive/impulsive, and oppositional symptom clusters [34] and evidence from both cognitive tests [37] and electrophysiology [38] supports this notion. Despite such analyses, surprisingly few clinical studies have evaluated actual methods to treat children with ADHD and comorbid ODD.

Two double-blind, placebo-controlled studies had been specifically designed to evaluate the efficacy of ATX in treating ODD symptoms in children with ADHD and comorbid ODD/CD, as measured by the ODD subscale of the investigator-rated Swanson, Nolan, and Pelham Rating Scale-Revised (SNAP-IV) [39].

In one study, ATX was superior in reducing ODD symptoms over time, significantly better at week 2 and week 5, but no longer at week 8 [40]. Thus, it remained uncertain whether ATX exerts a specific and enduring effect on ODD symptoms. Of note, the patient population in this study was restricted to patients with severe ADHD and ODD symptoms and poor Clinical Global Impressions (CGI) ratings.

The second study evaluated the efficacy of ATX in improving ADHD and ODD symptoms in pediatric patients with ADHD and comorbid ODD who were nonresponders to a previous parent training intervention [3]. In this 8-week study, both ADHD and ODD symptoms had significantly improved compared with placebo at the end of the 8-week double-blind treatment period. In addition, post-hoc analyses have also been conducted on data of the placebo-controlled core registration studies of ATX conducted in children and adolescents with ADHD [41]. In these studies, comorbid ODD was typically present in 30%–40% of patients, and ODD symptoms had been measured by the oppositional subscale of the Conners' Parent Rating Scale-Revised Short Form (CPRS-R:S). These post-hoc analyses had also given inconclusive results: A first subset analysis of 98 children with ADHD and comorbid ODD from two early placebo-controlled trials revealed significant improvement of ADHD symptoms, but no significant reduction of ODD symptoms versus placebo [42]. A second, more detailed subgroup analysis based on a larger placebo controlled ATX study in 226 chil-

Table 2 Treatment outcomes in ADHD comorbidities: studies comparison

Study Identifier (Author, Year)	*Study design, treatment duration*	*Age, Range (y)*	*Comparator regime*	*Atomoxetine dose*	*Co-morbid Disorder with ADHD*	*Co-morbid disorder outcome*
Kaplan et al. 2004	Randomized, double-blind. 9wk.	7-13	Placebo (n = 45)	Max. 2mg/kg/d or 90mg/d (n = 53)	ADHD+ODD	ATX significantly improved 3 of 4 CPRS subscales relative to PL: ADHD index (-7.7 vs -3.2; p = 0.005), cognitive (-4.1 vs -1.6; p = 0.006), hyperactive (-4.4 vs -1.3; p = 0.003) ATX was associated with nonsignificant reductions in the oppositional subscale (-2.4 vs -1.8 for PL)
Bangs et al. 2008,2006	Randomized. 8wk	Children	Placebo (n = 70)	1.2mg/kg/d (n = 156)	ADHD+ODD	ATX significantly improved SNAP oppositional subscale scores vs PL at wk 2 (15.4 vs 17.5; p = 0.003) and 5 (15.4 vs 16.8; p = 0.043), but not at wk 8 (15.6 vs 16.5; p = 0.209)
Newcorn et al. 2005	Randomized, double-blind 8wk	Mean 11.2	Placebo (n = 81)	0.5 (n = 44), 1.2 (n = 83) or 1.8 (n = 85)mg/kg/d bid	ADHD+ODD	ATX was associated with significant improvements in CPRS Oppositional subscale score at 0.5mg/kg/d (-3.4 vs -0.6; p = 0.04) and 1.8mg/kg/d (-3.4 vs -1.8; p = 0.027) but not at 1.2mg/kg/d (-2.2 vs -0.6; p = 0.32)
Kratochvil et al. 2005	Randomized, double-blind 8wk	7–17	ATX max. 1.8mg/kg/d bid + FLX 20mg/d od (n = 127)	Max. 1.8mg/kg/d bid (n = 46)	ADHD+ depressive or anxiety symptoms	ATX and ATX + FLX were each associated with marked improvements from baseline in CDRS-R total score (-17.6 and -20.4, respectively) and MASC score (-11.3 and -13.4, respectively)
Geller et al. 2007	Randomized, double-blind 12 wk	Children	Placebo (n = 89)	Max. 1.8mg/kg/d bid (n = 87)	ADHD+ anxiety disorder	ATX was associated with greater improvements than PL in MASC (-4.6 vs +2.1; p = 0.009) and CHQ-P-CFL (6.9 vs 3.3; p = 0.019) scores
Summer et al. 2006	Randomized, double-blind 12wk	Children	Placebo (n = 89)	Dosage not stated (n = 87)	ADHD+ anxiety disorder	ATX significantly improved PARS total scores (-5.5 vs -3.2; p = 0.011)

Y: year, **Wk**: week, **max**= maximum, **ODD**= oppositional defiant disorder, **ATX**: Atomoxetine, **PL**: Placebo , **ADHD-RS** = ADHD-Rating Scale; **ADHD-RS-IV** = ADHD-RS according to DSM-IV criteria, **CGI** = Clinical Global Impression, **CGI-ADHD-S** = CGI ADHD severity scale, **CPRS** = Conners' Parent Rating Scale, **SNAP**= Swanson, Nolan, and Pelham Rating Scale Revised
FLX = fluoxetine, **CDRS-R** = Children's Depression Rating Scale-Revised , **bid** = twice daily, **MASC**= Multidimensional Anxiety Scale for Children, **CHQ-P-CFL** = Child Health Questionnaire-
Parent-Completed Full Length **PARS** = Pediatric Anxiety Rating Scale

dren and adolescents with ADHD with and without comorbid ODD [25] concluded that ATX significantly reduced both ADHD and ODD symptoms and improved quality-of-life measures compared with placebo [43]. Data also suggested that the comorbid group may require higher ATX doses (1.8 mg/kg per day). In an additional post-hoc meta-analysis, acutephase data were analyzed from three double-blind placebo controlled ATX studies in 512 children and adolescents with ADHD (age 6–16 years); 158 had comorbid ODD. ATX significantly reduced ADHD symptoms in patients with and without ODD to a similar extent. However, the reduction of ODD symptoms in patients with comorbid ODD was not significantly higher than with placebo [45]. Finally, Cheng et al. (2007) performed a systematic meta-analysis on nine placebo-controlled ATX trials in children and adolescents (ATX 1,150, placebo 678 patients). In the smaller subgroup of comorbid ADHD/ODD patients, both ADHD and ODD symptoms were significantly reduced with ATX compared with placebo. Comorbid ODD status was significantly associated with smaller treatment-related reductions in ADHD symptoms. Cheng et al. concluded that ATX may have a role in treating comorbid ODD. In the light of these inconclusive results, additional prospective studies evaluating the efficacy and safety of ATX in pediatric patients with comorbid ADHD and ODD/CD are suggested.

Anxiety disorders

Pediatric anxiety disorders are the most common psychiatric disorders of childhood, affecting 8% to 21% of children [45]. Symptoms vary between individuals and can be expressed as a finger sucking, onychophagy, psychosomatic symptoms as a cefalea, abdominal pain, nauzea, sleep disturbances, tension, fatigue, „too good child"- when child is too quite, masturbation, encopresis, enuresis, conduct symptoms etc.

Comorbid anxiety disorder is estimated to occur in 25% to 35% of children with ADHD [41].

Investigators have noted higher rates of ADHD in children of parents with anxiety disorders than in children of comparison groups. Lahey et al. noted that children with diagnosis of attention deficit disorder without hyperactivity had higher rates of anxiety disorders than children with attention deficit hyperactivity disorder. A recent investigation of the familial interrelationship between attention deficit hyperactivity disorder and anxiety disorders provided evidence for an association between the two disorders. In 16-53% patients with generalized anxiety disorder (GAD) was found an evidence of existence of ADHD in childhood, compared to 2-9% in whole child population [46].

Milberger et al. (1995) examined the overlap between ADHD and generalized anxiety disorder in a clinical sample. For adults, when overlapping symptoms were subtracted, 75% of the sample still met criteria for ADHD, and 76% of the sample still met criteria for GAD. Thus, comorbidity between anxiety disorders and ADHD is not just an artifact of diagnostic overlap. Substantive hypotheses for the covariation between internalizing and externalizing disorders include where one disorder directly causes or contributes to another disorder. It is difficult to conceptualize how anxiety in a child could cause the development of ADHD; however it may be possible that anxiety alters the expression of ADHD. For example, children with comorbid ADHD and anxiety are often reported to be less impulsive than children with ADHD alone [47]. Alternatively, anxiety early in life might affect a child's ability to concentrate and finish schoolwork, and consequently may present with ADHD-type symptoms.

Furthermore, children with comorbid anxiety demonstrated a different pattern of responding to treatments leading to recommended modifications to treatments when comorbid anxiety is a factor [48]. Several studies have assessed the effects of mood or anxiety disorders in the treatment of ADHD. In youths with ADHD and comorbid anxiety, reports of trials with stimulants are inconsistent. Several reports have suggested diminished effectiveness and/or tolerability when monotherapy with stimulants was used in the treatment of ADHD comorbid with anxiety symptoms [49] or a diagnosis of an anxiety disorder [48, 49].

Diamond et al., however, reported similar tolerability and response to stimulant monotherapy in those with or without diagnosis of an anxiety disorder. Similarly, the MTA study found the response to stimulant monotherapy to be good irrespective of diagnosis with an anxiety disorder. Clinical practice shows, that stimulants can increase anxiety in some patients, so we have to consider ATX as a choice for treatment.

Systematic research about influence of ATX and methylphenydate on anxiety have not been performed (52), so next research is essential. We can mention only a few studies.

Geller et al. in a double-blind study compared atomoxetine with placebo for treating pediatric ADHD with comorbid anxiety, as measured by the ADHD Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IVPI) and the Pediatric Anxiety Rating Scale (PARS). Atomoxetine was efficacious in reducing ADHD symptoms in patients who have ADHD with comorbid anxiety and was well tolerated. There was also a significant reduction in independently assessed anxiety symptoms using both clinician-rated and self-rated measures, which merits further investigation. Results support consideration of atomoxetine for the treatment of ADHD in youths who have ADHD with comorbid anxiety disorder. Kratochvil et al. (51) assessed the safety and effectiveness of atomoxetine monotherapy compared with combined atomoxetine/ fluoxetine therapy in a population of children and adolescents with ADHD and concurrent symptoms of depression or anxiety. In pediatric patients with ADHD and comorbid symptoms of anxiety, atomoxetine monotherapy appears to be effective for treating ADHD. Up to date studies, as well as clinical practise show possibility of positive effect of ATX on anxiety with ADHD.

CONCLUSION

More than two-thirds of children with ADHD may have at least one co-morbid condition, and the presence of co-morbid conditions complicates the pharmacological management of individuals with ADHD. Despite this, there are relatively few systematic studies that specifically address the co-morbidity associated with ADHD. The majority of ADHD clinical studies in children and adolescents specifically exclude patients with co-existing disorder.Even though atomoxetine seems to be an effective and well tolerated option for ADHD treatment in the presence of co-morbid conditions. In spite of this, there are still some significant gaps in our knowledge of the most appropriate treatment options for ADHD with co-morbid conditions

In addition to improving symptoms of ADHD, findings suggest atomoxetine may improve symptoms of ODD, has a mild-to-moderate benefit on co-occurring symptoms of anxiety, and does not worsen tics in patients with Tourette's syndrome or chronic tic disorders Next research can reveal, if ODD and anxiety could be possible subtypes of ADHD what would bring a new perspective on disorder itself and efficient treatment.

These issues serve to emphasize the need for appropriate prospective clinical studies that are sufficiently powered, and that investigate different pharmacological approaches head to-head in patients with ADHD and co-existing co-morbid conditions.

REFERENCES

1. Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition? World Psychiatry. 2003; 2:104–113
2. Hechtman L. Assessment and diagnosis of attention-deficit/ hyperactivity disorder. Child Adolesc Psychiatr Clin N Am. 2000; 9:481–498
3. Dell'Agnello G, Maschietto D, Pancotto A, Calamoneri F, Masi G, Curatolo P, Besana D, Mancini F, Rossi A, Escobar R, Zuddas A. Atomoxetine hydrochloride in the treatment of children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: Results from a placebo-controlled Italian study. Eur Neuropsychopharmacol. 2009; 19: 822–834

4. Pactl et al. Hyperkinetická porucha a poruchy chování. 1st ed. Praha: Grada Publishing.2007; 240s.
5. Aosaki T, Graybiel AM, Kimura M. Effect of the nigrostriatal dopamine system on acquired neural responses in the striatum of behaving monkeys.Science. 1994; 265:412-415
6. Goldman-Rakic PS. Working memory dysfunction in schizophrenia.J Neuropsychiatry Clin Neurosci. 1994;6:348-357
7. Sawaguchi T, Matsumura M, Kubota K: Catecholaminergic effects on neuronal activity related to a delayed response task in monkey prefrontal cortex.J Neurophysiol.1990; 63:1385-1400
8. Aston-Jones G, Bloom FE: Norepinephrine containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli.J Neuroscience.1981;1:887-900
9. MTA Cooperative Group.Arch Gen Psychiatry. 1999; 56: 1073-86
10. Conley R, Gupta SK, Sathya G. Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form.Curr Med Res Opin. 2006; 22(10):1879-92
11. Volkow N. et al. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. Am J Psychiatry. 1999; 156 (1):19-26
12. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behav Brain Res. 1998; 94: 127-52
13. Wigal S B. Efficacy and Safety Limitations of Attention-Deficit Hyperactivity Disorder Pharmacotherapy in Children and Adults, CNS Drugs. 2009; 23 (1): 21
14. Greydanus DE, Pratt HD, Patel DR. Attention deficit hyperactivity disorderacross the lifespan: the child, adolescent, and adult. Dis Mon .2007; 53 (2): 70-13.
15. Barton J. Atomoxetine: a new pharmacotherapeutic approach in the management of attention deficit/hyperactivity disorder. Arch Dis Child. 2005; 90:26-9.
16. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology.2002; 27(5): 699-71.1
17. Gehlert DR, Schober DA, Gackenheimer SL. Comparison of (R)-[‘H]tomoxetine and (R/S)-[‘H]nisoxetine binding in rat brain. J Neurochem. 1995; 64 (6): 2792-800.
18. Wernicke JF, Faries D, Girod D, et al. Cardiovascular effects of atomoxetine in children, adolescents, and adults. Drug Saf. 2003; 26(10): 729-40.
19. Spencer TJ, Kratochvil CJ, Sangal RB, et al. Effects of atomoxetine on growth in children with attention-deficit/hyperactivity disorder following up to five years of treatment. J Child Adolesc Psychopharmacol. 2007; 17(5): 689-700.
20. Sangal RB, Owens J, Allen AJ, et al. Effects of atomoxetine and methylphenidat on sleep in children with ADHD. Sleep. 2006; 29(12): 1573-85.
21. Witcher JW, Long A, Smith B, et al. Atomoxetine pharmacokinetics in children and adolescents with attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol. 2003; 13: 53-63.
22. Eli Lilly and Company. Atomoxetine (Strattera™) prescribing information [online]. Available from URL: http://pi.lilly.com/tis/strattera-pi.pdf [Accessed 2009 Feb 9].
23. Sauer J.M., Ring B.J., Witcher J.W. Clinical pharmacokinetics of atomoxetine. Clin Pharmacokinet. 2005; 44:571–590.
24. Michelson D. et al. Addition of atomoxetine for depression incompletely responsive to sertraline: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007; 68:582–587.
25. Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, Newcorn J, Sallee RF, Sangal RB, Saylor K, West S, Kelsey D, Wernicke J, Trapp NJ, Harder D.Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: A randomized, placebo-controlled study. Am J Psychiatry.2002;159:1896–1901
26. Jensen PS, Hinshaw SP, Kraemer HC, Lenora N, Newcorn JH, Abikoff HB, March JS, Arnold LE, Cantwell DP, Conners CK, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Pelham WE, Severe JB, Swanson JM, Wells KC, Wigal T, Vitiello B. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry. 2001; 40:147–158
27. Kuhne M, Schachar R, Tannock R. Impact of comorbid oppositional or conduct problems on attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 1197; 36:1715–1725
28. Raine A, Venables PH, Williams M. Relationships between central and autonomic measures of arousal at age 15 years and criminality at age 24 years. Arch Gen Psychiatry. 1990;47:1003–7.
29. AACAP Official Action.. Practice parameters for the assessment and treatment of children and adolescents with conduct disorder. J Am Acad Child Adolesc Psychiatry. 1997:36:122–39.
30. Lahey BB, Hart EL, Pliszka S, Applegate B, McBurnett K. Neurophysiological correlates of conduct disorder: a rationale and a review. J Clin Child Psychol. 1993;22:141–53.
31. Masi G, Manfredi A, Milone A. Predictors of nonresponse to psychosocial treatment in children and adolescents with disruptive behavior disorders. **J Child Adolesc Psychopharmacol**. 2011; 21:51-55.
32. American Academy of Child & Adolescent Psychiatry (AACAP). Preventive effects of treatment of disruptive behavior disorder in middle childhood on substance use and delinquent behavior. Journal of the American Academy of Child and Adolescent Psychiatry. 2007; *46* (1): 33-39.

33. Sondeijker FEPL, Ferdinand RF, Oldehinkel AJ, Veenstra R, De Winter AF, Ormel J, Verhulst FC. Classes of adolescentswith disruptive behaviors in a general population sample. Soc Psychiatry Psychiatr Epidemiol. 2005; 40:931–938
34. Burns GL, Walsh JA. The influence of ADHD-hyperactivity/ impulsivity symptoms on the development of oppositional defiant disorder symptoms in a 2-year longitudinal study. J Abnorm Child Psychol. 2002; 30:245–256
35. Chen TJH, Blum K, Mathews D, Fisher L, Schnautz N, Braverman ER, Schoolfield J, Downs BW, Comings DE. Are dopaminergic genes involved in a predisposition to pathological aggression? Hypothesizing the importance of "super normal controls" in psychiatricgenetic research of complex behavioral disorders. Med Hypotheses. 2005;65:703–707
36. Comings DE, Chen C, Wu S, Muhleman D. Association of the androgen receptor gene (AR) with ADHD and conduct disorder. Neuroreport. 1999; 10:1589–1592
37. Oosterlaan J, Scheres A, Sergeant JA.Which executive functioning deficits are associated with AD/HD, ODD/CD and comorbid AD/HD+ODD/CD? J Abnorm Child Psychol.2005; 33:69–85
38. Baving L, Rellum T, Kaucht M, Schmidt MH.Children with oppositional-defiant disorder display deviant attentional processingindependent of ADHD symptoms. J Neural Transm.2006;113:685–69
39. Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, Clevenger W, Davies M, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Jensen PS, March JS, Newcorn JH, Owens EB, Pelham WE, Schiller E, Severe JB, Simpson S, Vitiello B, Wells K, Wigal T, Wu M: Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry.2001;40:168–179
40. Bangs ME, Hazell P, Danckaerts M, Hoare P, Coghill DR, Wehmeier PM, Williams DW, Moore RJ, Levine L; Atomoxetine ADHD/ODD Study Group: Atomoxetine for the treatment of attentiondeficit/ hyperactivity disorder and oppositional defiant disorder. Pediatrics.2008; 121:314–20
41. Kelsey DK, Sumner CR, Casat CD, Coury DL, Quintana H, Saylor KE, Sutton VK, Gonzales J, Malcolm SK, Schuh KJ, Allen AJ. Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebocontrolled trial. Pediatrics.2004; 114(1):1–8
42. Kaplan S, Heiligenstein J, West S, Busner J, Harder D, Dittmann R, Casat C, Wernicke JF. Efficacy and safety of atomoxetine in childhood attention-deficit/hyperactivity disorder with comorbid oppositional defiant disorder. J Atten Disord. 2004; 8:45–52
43. Newcorn J, Spencer TJ, Biederman J, Milton DR, Michelson D. Atomoxetine treatment in children and adolescents with attentiondeficit/ hyperactivity disorder and comorbid oppositional defiant disorder. J Am Acad Child Adolesc Psychiatry.2005; 44:240–248
44. Biederman J, Spencer TJ, Newcorn JH, Gao H, Milton DR, Feldman PD, Witte MM: Effect of comorbid symptoms of oppositional defiant disorder on responses to atomoxetine in children with ADHD: A meta-analysis of controlled clinical trial data. Psychopharmacology.2007; 190:31–41
45. Anderson et al. Arch Gen Psychiatry.1987; 44(1):69 -76
46. Jennifer SB, Mark RD . Examining Alternative Explanations of the Covariation of ADHD and Anxiety Symptoms in Children. A Community Study J Abnorm Child Psychol. 2008; 36:67–79
47. Pliszka SR. Effect of anxiety on cognition, behavior, and stimulant response in ADHD. Journal of American Academy of Child & Adolescent Psychiatry.1989; 28:882–887
48. Costin J, Vance A, Barnett R, O'Shea M, Luk E. Attention deficit hyperactivity disorder and comorbid anxiety:Practitioner problems in treatment planning. Child & Adolescent Mental Health, 2002; 7:16–24
49. Taylor E, Schachar R, Thorley G, Wieselberg HM, Everitt B, Rutter M. Which boys respond to stimulant medication? A controlled trial of MPH in boys with disruptive behavior. Psychol Med.1987;17:121-143
50. Diamond IR, Tannock R, Achachar RJ. Response to methylphenidate in children with ADHD and comorbid anxiety. J Am Acad Child Adolesc Psychiatry. 1999; 38:402-409
51. Kratochvil, Newcorn, Arnold L, Duesenberg, Emslie, Quintana, Sarkis, Wagner, GaoAO, Michelson, Biederman. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety aymptoms. J. Am. Acad. Child Adolesc. Psychiatry. 2005; 44(9): 915-24
52. Cheng JY, Chen RY, Ko JS, Ng EM. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. Psychopharmacology. 2007; 194:197–209
52. Geller, Donnelly, Lopez, Rubin, Newcorn, Sutton, Bakken, Packowski, Kelsey, Sumner. Atomoxetine treatment for pediatric patients with attention-deficit/hyperactivity disorder with comorbid anxiety disorder. J. Am. Acad. Child Adolesc Psychiatry. 2007;46(9): 1119
53. Milberger S, Biederman J, Faraone SV, Murphy J, Tsuang MT. Attention deficit hyperactivity disorder and comorbid disorders: Issues of overlapping symptoms. American Journal of Psychiatry.1995; 152: 1793–1799

Received: July, 19, 2012
Accepted: September, 20, 2012