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Research article

Evaluating clonidine response in children and adolescents with attention-deficit/hyperactivity disorder

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood, which is generally treated with stimulant and non-stimulant medications. However, 10–30% of patients in clinical setting do not present with adequate response to initial stimulant treatment. Thereby, clonidine may be considered for those patients who have failed to respond to psychostimulant/atomoxetine monotherapy or as an augmentation for inadequate response/comorbidity. This observational study evaluated its effectiveness as a single drug in ADHD cases unresponsive to previous treatment trials. Seventeen ADHD cases that were non-responders to stimulant, non-stimulant and combination therapy for the primary symptoms of ADHD were included in the study. Four cases dropped out before follow up, leaving thirteen cases who were administered immediate release clonidine treatment alone with a mean dose of 0.2 ± 0.05 mg/day at baseline. The trial lasted for 12 weeks, and treatment outcomes were evaluated by the Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S) and the Clinical Global Impressions-Severity (CGI-S) and Improvement (CGI-I) scales. Mean age of the sample was 12.5 years (SD = 3.0) and eleven of the subjects had another comorbid psychopathology. Only two

cases were evaluated as “very much improved”, while another patient was judged to be “minimally improved” after 12 weeks of clonidine treatment. Attrition during follow-up was associated with higher median scores on the hyperactivity and impulsivity subscales (Mann-Whitney U test, p = 0.02). According to the T-DSM-IV-S, CGI-S, and CGI-I scales, clonidine treatment by itself had minimal benefits in this sample of treatment of refractory cases with ADHD evaluated at the study center. Clonidine is not available in Turkey pharmaceutical marketing system and patients’ access to drug is limited. Our results provide first data regarding the use of clonidine in Turkish ADHD patients.

Keywords: Alpha-2 adrenergic receptor agonist; Attention-Deficit/Hyperactivity Disorder; Clonidine

Abbreviations: T-AD: Attention-deficit subscale; T-HIP: Hyperactivity/impulsivity subscale; ODD: Oppositional defiant disorder subscale; CD: Conduct disorder subscale; CGI-S: Clinical Global Impressions-Severity scale

1. Introduction

ADHD is a common childhood neurodevelopmental disorder that affects around 5.2% of children worldwide [1]. The disorder is marked by inattention, hyperactivity, and/or impulsivity that can seriously impair emotional, educational, and social development in children. Male children are twice as likely to be diagnosed as similarly aged females. However, this may be due to males expressing more hyperactive symptoms, while females demonstrate inattentiveness more often, which may be harder to detect [2]. ADHD is also often comorbid with oppositional defiant disorder, tic disorder, conduct disorder, anxiety disorder, and autism. It often requires multi-modal treatments, including both behavioral and pharmacological treatments such as stimulants and non-stimulant medications [2,3]. Among those medications, psychostimulants are the most widely prescribed pharmacologic treatment for ADHD around the world [4,5]. While psychostimulants are prescribed as first-line treatment for a significant number of patients, ADHD symptoms can remain uncontrolled by psychostimulants in 10% to 30% of patients [4–7]. Furthermore, psychostimulant effectiveness may be restricted by side effects and tolerability issues, such as weight loss and sleep problems in children [8]. For those patients, the availability of alpha-2 adrenergic receptor agonists, such as clonidine, for the treatment of ADHD increases the prospect of better ADHD control and comorbid disorders such as tic disorders, sleep disorders and conduct disorders [9–11].

Previous studies on the efficacy of alpha-2 adrenergic receptor agonists were conducted mostly in the US and clinical experience with those agents in Turkey has been very limited. Therefore, the goal of the present study was to evaluate the efficacy of clonidine as a single agent in methylphenidate/atomoxetine-resistant ADHD cases diagnosed at a single tertiary treatment center in Turkey.

2. Material and methods

2.1. Sample

This study was conducted between January 2012 and August 2015 at the Malatya State Hospital's Child and Adolescent Psychiatry Clinic. Inclusion criteria were being diagnosed with ADHD according to Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) criteria, having received at least one prior stimulant and non-stimulant prescription alone or together at an adequate dose (1.2 mg/kg/day for stimulants, 1.4 mg/kg/day for atomoxetine) for an adequate duration (>three months) but without response (<20.0% change in parent and teacher reports) and providing informed consent for study (for parents) and written assent for children. Apart from the presence of psychosis and chronic medical disorders requiring treatment (such as asthma, epilepsy and celiac disease) no criteria were set for exclusion. Within the study period 357 patients with ADHD were evaluated at the study center and pharmacotherapy was provided for 67.2% (n = 240). Forty-one of the patients (16.6%) were classified as treatment resistant and approached for inclusion. Fifteen of the patients were excluded due to chronic medical disorders (Seven with asthma, four with epilepsy and one with abnormalities in the electroencephalogram, three with celiac disease) while parents of the remaining nine patients refused participation. Seventeen patients were judged to be eligible at baseline and cardiologic evaluations were planned prior to clonidine treatment. Four of the patients were lost to follow-up at this stage leaving thirteen patients.

0.1 mg immediate release (IR) clonidine tablets were prescribed to these patients which were brought from abroad by the Ministry of Health via direct international import route. Clonidine was planned to be given at a dose of 0.05 mg daily at the beginning and then gradually increased to two divided doses with a maximum dose being 0.4 mg. The duration of treatment was 12 weeks. The cases were evaluated at baseline, and at the end of the 12th week of treatment. Ethical approval was obtained from Turkish Ministry of Health and Malatya Training and Research Hospital for the present study (Ethical Committee approval number: 59728196/640/12073).

2.2. Instruments

Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S): This scale was completed by the parents to determine the severity of ADHD in children. The T-DSM-IV-S was developed to assess symptoms of disruptive behavior disorders according to DSM-IV criteria. It includes 9 items related to attention-deficit, 9 items related to hyperactivity, 3 items related to impulsivity, 8 items related to oppositional defiant disorder (ODD), and 15 items related to conduct disorder (CD). All questions were answered on a Likert scale with 4 categories according to severity (i.e., 0 = absent, 1 = low, 2 = high, 3 = very high). The scale was found to be reliable and valid in previous studies [12]. In the present study, the internal consistency of the scale was found to be quite high (Cronbach alpha coefficient = 0.899).

Clinical Global Impressions Scale: This scale was developed for use in clinical studies. It has 3 domains evaluating the severity of disorder, magnitude of improvement with treatment, and adverse effects. Only the severity and improvement scales were used in the present study.

For severity (CGI-S), the subject with psychopathology was scored by a clinician on a scale from 1 to 7 according to the severity of disorder at the time of observation (1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = extremely ill). Improvement (CGI-I) was also scored by the clinician on a scale from 1–7 according to the change in health status from the onset of the study (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse).

2.3. Statistical analyses

Statistical analyses were performed using the SPSS v.22.0 statistical package. Wilcoxon tests were used to compare before- and after-treatment scores, and the Mann-Whitney U test was used to compare two independent groups, because the data were not normally distributed. Categorical variables were analyzed with the Fisher-Freeman-Halton test. Statistical significance level was considered as $p < 0.05$.

3. Results

Seventeen children and adolescents (fourteen boys) were included. Most of the children (n = 12) were in primary school, and the remainder was in high school. Mean and median age of the cases were 12.5 (SD = 3.0) and 12.0 (Inter quartile range, IQR = 5.0) respectively. Most of the cases were born at term and without complications during labor (n = 11). In eleven cases, there was a comorbid psychiatric disorder and in one case there was one medical comorbid disorder. Comorbid diagnoses of the cases are summarized in Table 1.

Table 1. The comorbid diagnoses of cases diagnosed with ADHD given open-ended, prospective clonidine treatment, according to sex.

Comorbid diagnosis (n, %)	Boys (n = 9)	Girls (n = 2)	Overall (n = 11)
Tic disorders	4 (44.4%)	1 (50.0%)	5 (45.5%)
Conduct disorder	3 (33.3%)	0 (0.0%)	3 (27.3%)
Any Anxiety disorder	0 (0.0)	1 (50.0%)	1 (9.1%)
Obsessive Compulsive Disorder	1 (11.1%)	0 (0.0%)	1 (9.1%)
Mental Retardation*	1 (11.1%)	0 (0.0%)	1 (9.1%)

* IQ < 70 as evaluated with the Turkish version of WISC-R (Savasir I, Sahin N. Manual for the Wechsler Intelligence Scale for Children- Revised (WISC-R). Turkish Psychologists' Association Press, Ankara 1995).

In most cases, both parents had a high school or more advanced education (n = 12). The fathers were mostly civil servants (n = 7). Five mothers and two fathers had psychiatric disorders and were undergoing treatment. Three were relatives rather than biological parents. Cases were evaluated using T-DSM-IV-S completed by the parents before treatment and at the 12th week of treatment, and the CGI-S and CGI-I were completed by the clinician. The scores of cases before and after treatment are outlined in Table 2. Median and mean doses of clonidine at baseline and at the 12th week of treatment respectively were 0.5 and 0.06 mg/day (SD = 0.02 mg/day) and 0.2 and 0.2 mg/day (SD = 0.06 mg/day). When CGI-S and T-DSM-IV-S test scores of the cases before and after treatment were evaluated with the Wilcoxon test, no statistically significant difference was found. When the CGI-I scale was evaluated, only three patients were found to have benefited from clonidine (Table 3). Importantly, all these patients were male. One had obsessive-compulsive disorder as a comorbid disorder with ADHD. Another with a conduct disorder benefited greatly from treatment and a patient with a tic disorder showed improvement. Four cases dropped out of the follow-up and

treatment process during the study; their median scores from the hyperactivity and impulsivity subscale were found to be significantly higher than those of the rest of the cases (p = 0.023) (Table 4). Eight cases reported side effects with clonidine treatment. Side effects by order of frequency were as follows: Sedation (n = 4), nausea/vomiting (n = 2), vertigo and increased hyperactivity (for both; n = 1). Chi-square test found no significant relation between the presence of side effects and dropping out from treatment (p = 0.893).

Table 2. Comparison of psychometric measurements in ADHD cases, before and after treatment with clonidine.

Scale	Prior to treatment	After treatment	p*
	Median (IQR)	Median (IQR)	
T-AD	0 (0–3)	0 (0–4)	0.27
T-HI	7 (3–9)	8 (2–9)	0.59
T-ODD	8 (4–8)	8 (7–8)	0.19
T-CD	15 (14–15)	15 (14–15)	0.32
T-overall	29 (23–33)	31 (25–36)	0.44
CGI-S	5 (4–6)	4 (4–5)	0.02

* Wilcoxon test.

Table 3. CGI-I values at the 12th week of treatment.

	Score	n (%)
CGI-I	1 = very much improved	1 (7.7)
	2 = much improved	1 (7.7)
	3 = Minimally improved	1 (7.7)
	4 = no change	8 (47.1)
	5 = Minimally worse	2 (11.8)

CGI-I: Clinical Global Impressions Scale, Improvement.

Table 4. Comparison of psychometric measurements in ADHD cases who dropped out of clonidine treatment with those who continued treatment.

Scale	Continued treatment	Dropped out from treatment	p*
	Median (IQR)	Median (IQR)	
T-AD	0 (0–3)	1 (0–4)	0.55
T-HIP	7 (3–9)	1 (0–2)	0.02
T-ODD	8 (4–8)	6 (3–8)	0.48
T-CD	15 (14–15)	15 (14–15)	0.96
T-overall	29 (23–33)	24 (17–26)	0.13
CGI-S	5 (4–6)	-	-

* Mann-Whitney U test.

4. Discussion

As far as we are aware, this is the first open-label study of clonidine on children with treatment refractory ADHD reported from Turkey. Even with a broad range of definitions for improvement, only three of the sample benefited from treatment according to the clinician's judgment, while parental reports showed no benefit. Adverse effects were also frequent. Previous studies showed that although stimulants are the primary therapy for patients with ADHD, adverse events, comorbidities, contraindications, partial responses, and lack of response might restrict their use in some patients [9,13–15]. Alpha-2 agonists, IR clonidine and guanfacine, which are used for blood pressure control, were used off-label as second-line agents for patients who failed to respond to psychostimulants or as adjunctive therapy for patients with suboptimal results with a psychostimulant alone [6,16,17]. Clonidine has also been shown to be beneficial for CD, ODD, tic disorder, sleep problems, mental retardation and anxiety disorder, which are comorbid with ADHD [3,9,18–21]. A systematic review and meta-analysis of 12 placebo-controlled trials of alpha-2 agonists as monotherapy or augmentation was recently carried out to evaluate the safety and efficacy of alpha-2 agonists in ADHD in children and they were proved to be superior to placebo as monotherapy and to a lesser degree as co-treatment [22]. Another meta-analysis of 11 small double-blind and open-label studies reviewing the effect of immediate-release clonidine on symptoms of ADHD alone or with comorbidities determined a moderate overall effect size [1]. But when comparing the alpha-2 agonists to psychostimulants as monotherapy for ADHD, the alpha-2 agonists did not perform nearly as well. Evaluations have demonstrated that clonidine and guanfacine are around 40% to 75% as effective as psychostimulants in managing the primary symptoms of ADHD [23,24].

In the present study, cases were evaluated before and at the 12th week of the study with T-DSM-IV-S completed by parents and the CGI-S and CGI-I scales completed by a clinician. No significant differences were seen in the CGI-S or T-DSM-IV-S test results before and after treatment. The results of this study showed that clonidine is not effective as a single agent in children and adolescents with ADHD who had at least one stimulant and non-stimulant prescription alone or together before and did not respond these medications for primary symptoms of ADHD. All cases in the present study were difficult ones who had undergone stimulant and atomoxetine treatment alone or in combination in our clinic for a mean of two years at adequate doses and duration, but without improvement in ADHD symptoms. This duration may be due to the features of clinical practice in our country and may have affected our results. According to the prevalent practice of child and adolescent psychiatrists in Turkey, stimulants are frequently the first step in treatment of ADHD which is continued for three months with upward titration of dose. An unsuccessful trial of one type of stimulant leads to a trial with another form (i.e. long acting) and atomoxetine is usually reserved for the third step. Children and their families are usually not brought for treatment during the summer which forces clinicians to repeat the steps for the successive school semester and attempting to combine atomoxetine and stimulants as a last resort.

Also, most patients had other comorbid disorders. As shown in previous studies, the heterogeneous nature of ADHD symptoms, comorbidities, and pharmacogenetics of patients may have led to poor outcomes for all medications [25–27]. In addition, previous studies have reported various reasons for non-adherence to medication in ADHD such as male gender, severe ADHD

symptoms, oppositional-defiant symptoms, and parental opposition to use of medication as well as side effects [28,29].

In the present study, four cases dropped out from treatment during the study. Three out of these four cases were male, and their files reported that they were reluctant to engage in more treatment and felt hopeless, since they failed to benefit from their previous treatments. These four cases had also significantly higher median scores on the hyperactivity and impulsivity scale (p = 0.023) than the rest of the cases at the beginning of the study. In addition, eight cases reported side effects from clonidine treatment. Side effects by order of frequency were as follows: Sedation (n = 4), nausea/vomiting (n = 2), vertigo and increased hyperactivity (for both; n = 1). No significant relation was found between the presence of side effects and the rate of dropping out from the study (p = 0.893) like other studies [10]. In other related studies, the IR formulation of clonidine had adverse effects including somnolence, sedation, drowsiness, and irritability. IR clonidine has a relatively short half-life, and the need for frequent dosing may have led to increased side effects [10,14–16,20,23].

Unfortunately, clonidine is not available in Turkey. In these resistant cases, IR clonidine could be imported with the approval of the Ministry of Health. We could not get Ministry of Health approval to import the drug for patients other than the 17 patients mentioned in the study (i.e. on children with less severe symptoms and greater response to previous treatments). Hence, we could use it only on these patients between these years. This was an important limitation of the study. Another limitation was that this was an uncontrolled study with a short duration of follow-up. A longer follow-up may have provided greater information on long term effects of clonidine treatment. Further limitations include lack of teacher observations and objective evaluations of treatment effects (e.g. with neuropsychological tests). Additional treatment studies with larger populations are warranted in Turkey about the effects of clonidine, especially since the US Food and Drug Administration approved the extended release form for children and adolescents with ADHD. Therefore, we believed that this drug should be more easily available for Turkish patients. Further studies are required to compare alpha-2 agonists head-to-head with psychostimulants and with atomoxetine.

5. Conclusions and clinical significance

As far as we are aware, this is the first longitudinal, naturalistic, open-label study of clonidine on children with treatment refractory ADHD reported from Turkey. According to the T-DSM-IV-S, CGI-S, and CGI-I scales, clonidine treatment by itself had minimal benefits in this sample of treatment of refractory cases with ADHD evaluated at the study center. Previous studies on the efficacy of alpha-2 adrenergic receptor agonists were conducted mostly in the US, and clinical experience with those agents in Turkey has been very limited and our results should be replicated with larger studies from multiple centers in our country.

Conflict of interest

All authors declare no conflicts of interest in this paper.

References

1. Polanczyk G, Lima MD, Horta B, et al. (2007) The worldwide prevalence of ADHD: A systematic review and Metaregression analysis. *Am J Psychiatry* 164: 942–948.
2. Ramtekkar UP, Reiersen AM, Todorov AA, et al. (2010) Sex and age differences in attention-deficit/Hyperactivity disorder symptoms and diagnoses: Implications for DSM-V and ICD-11. *J Am Acad Child Psy* 49: 217–228.
3. Wolraich M, Brown L, Brown R, et al. (2011) Subcommittee on attention- deficit/hyperactivity disorder; steering committee on quality improvement and management. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children. *Pediatrics* 128: 1007–1022.
4. Willens T, Spencer T (2000) The stimulants revisited. *Child Adolesc Psychiatr Clin N Am* 9: 573–603.
5. Golmirzaei J, Mahboobi H, Yazdanparast M, et al. (2016) Psychopharmacology of attention-deficit Hyperactivity disorder: Effects and side effects. *Curr Pharm Design* 22: 590–594.
6. Pliszka S (2007) Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/Hyperactivity disorder. *J Am Acad Child Psy* 46: 894–921.
7. Briars L, Todd T (2016) A review of pharmacological management of attention-deficit/Hyperactivity disorder. *J Pediatr Pharmacol Ther* 21: 192–206.
8. Barbaresi WJ, Katusic SK, Colligan RC, et al. (2006) Long-term stimulant medication treatment of attention-deficit/Hyperactivity disorder. *J Dev Behav Pediatr* 27: 1–10.
9. Connor DF, Barkley RA, Davis HT (2000) A pilot study of Methyiphenidate, Clonidine, or the combination in ADHD Comorbid with aggressive Oppositional defiant or conduct disorder. *Clinical Pediatrics* 39: 15–25.
10. Palumbo DR, Sallee FR, Pelham WE, et al. (2008) Clonidine for attention-deficit/Hyperactivity disorder: I. Efficacy and Tolerability outcomes. *J Am Acad Child Psy* 47: 180–188.
11. Leckman JF (1991) Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 48: 324.
12. Turgay A (1994) Disruptive behavior disorders child and adolescent screening and rating scales for children, adolescents, parents and teachers. West Bloomfield (Michigan): Integrative Therapy Institute Publication.
13. Hunt RD, Minderaa RB, Cohen DJ, et al. (1985) Clonidine benefits children with attention deficit disorder and Hyperactivity: Report of a double-blind placebo-crossover therapeutic trial. *J Am Acad Child Psy* 24: 617–629.
14. Agarwal V, Sitholey P, Kumar S, et al. (2001) Double-blind, placebo-controlled trial of Clonidine in hyperactive children with mental retardation. *Ment Retard* 39: 259–267.
15. Hazell PL, Stuart JE (2003) A Randomized controlled trial of Clonidine added to Psychostimulant medication for hyperactive and aggressive children. *J Am Acad Child Psy* 42: 886–894.
16. Connor DF, Fletcher KE, Swanson JM (1999) A Meta-Analysis of Clonidine for symptoms of attention-deficit Hyperactivity disorder. *J Am Acad Child Psy* 38: 1551–1559.
17. Martinez-Raga J, Knech C, Szerman N, et al. (2012) Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. *CNS Drugs* 27: 15–30.

18. Borison RL, Ang L, Hamilton WJ, et al. (1983) Treatment approaches in Gilles de la Tourette syndrome. *Brain Res Bull* 11: 205–208.
19. Gaffney GR, Perry PJ, Lund BC, et al. (2002) Risperidone versus Clonidine in the treatment of children and adolescents with Tourette's syndrome. *J Am Acad Child Psy* 41: 330–336.
20. Schvehla TJ, Mandoki MW, Sumner GS (1994) Clonidine therapy for Comorbid attention-deficit Hyperactivity disorder and conduct disorder: Preliminary findings in a Children's inpatient unit. *South Med J* 87: 692–695.
21. Spencer TJ, Kratochvil CJ, Sangal RB, et al. (2007) Effects of Atomoxetine on growth in children with attention-deficit/Hyperactivity disorder following up to five years of treatment. *J Am Acad Child Psy* 17: 689–699.
22. Hirota T, Schwartz S, Correll CU (2014) Alpha-2 Agonists for attention-deficit/Hyperactivity disorder in youth: A systematic review and Meta-Analysis of Monotherapy and add-on trials to stimulant therapy. *J Am Acad Child Psy* 53: 153–173.
23. Jain R, Segal S, Kollins SH, et al. (2011) Clonidine extended-release tablets for pediatric patients with attention-deficit/Hyperactivity disorder. *J Am Acad Child Psy* 50: 171–179.
24. Sallee FR, Eaton K (2010) β-Guanfacine extended-release for attention-deficit/hyperactivity disorder (ADHD). *Expert Opin Pharmacother* 11: 2549–2556.
25. Froehlich TE, McGough JJ, Stein MA (2010) Progress and promise of attention-deficit hyperactivity disorder pharmacogenetics. *CNS Drugs* 24: 99–117.
26. Tan-Kam T, Suthisisang C, Pavasuthipaisit C, et al. (2013) Importance of pharmacogenetics in the treatment of children with attention deficit hyperactive disorder: A case report. *Pharmacogenomics Pers Med* 6: 3–7.
27. Danckaerts M, Sonuga-Barke EJS, Banaschewski T, et al. (2009) The quality of life of children with attention deficit/hyperactivity disorder: A systematic review. *Eur Child Adolesc Psychiatry* 19: 83–105.
28. Gau SSF, Shen HY, Chou MC, et al. (2006) Determinants of adherence to methylphenidate and the impact of poor adherence on maternal and family measures. *J Am Acad Child Psy* 16: 286–297.
29. Charach A, Ickowicz A, Schachar R (2004) Stimulant treatment over five years: Adherence, effectiveness, and adverse effects. *J Am Acad Child Psy* 43: 559–567.

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