

Agomelatine Augmenting Partial Stimulant Response in ADHD and Mitigating Stimulant-induced Insomnia and Anxiety

Ahmed Naguy^{1*} and Ali Al-tajali²

¹Child and Adolescent Psychiatrist, Kuwait Centre for Mental Health (KCMH), Kuwait

²General Adult Psychiatrist, Neuromodulation & Psych Rehab, KCMH, Kuwait

*Corresponding author: Ahmed Naguy, Department of Child and Adolescent Psychiatry, Kuwait Centre for Mental Health (KCMH), Kuwait, Tel: +965/65541937; E-mail: ahmednaguy@hotmail.co.uk

Received date: April 22, 2015, Accepted date: May 14, 2015, Published date: May 21, 2015

Copyright: © 2015 Naguy A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Attention deficit hyperactivity disorder (ADHD) is amenable to successful pharmacologic treatment with stimulants being first-line. Stimulants are generally safe but could be associated with some adverse effects such as insomnia and anxiety exacerbation in this population, both of which could jeopardize treatment-adherence and blunt the therapeutic response.

Here, we are reporting a 13-year-old case of severe ADHD with mediocre response to an adequate trial of methylphenidate with stimulant-related anxiety and insomnia that robustly showed marked cognitive improvement and amelioration of both anxiety and insomnia after augmentation with agomelatine with great safety and tolerability.

Keywords: Agomelatine; ADHD; Stimulant-related anxiety; Insomnia

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly encountered child and adolescent psychiatric disorders in clinical practice with a worldwide prevalence of circa 5% [1], ranging from 3-9% depending on the employed diagnostic criteria. ADHD is amenable to successful pharmacologic treatment with stimulants being first-line in guidelines. Yet, 20-35% of subjects in clinical trials showing inadequate response that could be attributed in part to dose-limiting side effects of medications or disorder severity or complexity [2]. Stimulants are generally safe but could be associated with a number of adverse effects such as insomnia [3] Stimulant-related anxiety exacerbation is commonly cautioned in this population [4].

Stimulants are the mainstay of treatment [5] with effect sizes of 0.8-1.1, and literature is highly consistent on the effectiveness of stimulant medications and behavioral interventions in the management of the core symptoms of ADHD [6].

Common side effects seen with psychostimulants are insomnia, headache, irritability, agitation, nervousness, tremor, loss of appetite, nausea and weight loss. These tend to be mild, dose dependent and transitory but sometimes dose-limiting and too difficult to tolerate [7] compromising treatment-adherence and blunting therapeutic response. Patients with less than optimal response to one stimulant, should undergo a trial of another stimulant category with better outcome [8]. Here, we are reporting a case, 13-year-old, with ADHD-severe inattentive presentation (IA) that failed a trial of atomoxetine, showed partial response over methylphenidate that soon blunted coupled with treatment-emergent insomnia and prominent anxiety symptoms. Insomnia, anxiety and less impressive cognitive response could have been addressed successfully pharmacologically with clonidine augmentation. But parents' apprehensive concerns about

reported cardiovascular fatalities of stimulant-clonidine combinations were overwhelming and counterproductive. Agomelatine is a novel antidepressant with unique actions (MASSA; melatonergic agonist, specific serotonergic antagonist) [9].

Melatonergic and chronobiotic actions would help with sleep problems without compromising daytime vigilance and 5HT_{2c} antagonism would impart PFC-NDDI (Norepinephrine-Dopamine disinhibition) procognitive properties to this drug portfolio. In theory, this seems appealing and neatly fitting the neurobiological underpinnings of ADHD. After parents' psycho-education, regarding pros and cons of the medication trial, and written consent obtained, agomelatine augmentation was pursued in this case with very impressive response as regards ADHD core symptoms and favorably ameliorated methylphenidate-related insomnia and anxiety.

Case Presentation

A 13-year-old female Kuwaiti youngster presented to our OPD clinic in accompaniment of her parents for evaluation of scholastic difficulties and some behavioural problems. She ranks the Third amongst 5 sibs emanating from non-consanguineous monogamous family. She is the product of noncomplicated elective Caesarean Section with normal developmental milestones. As a toddler, parents retrospectively can recall that she was fussy and colicky, adventurous and curious exploring the surroundings, impersistent at toy playing and displaying excessive tantrums. She had episodic bronchial asthma that seems to be outgrown by now. She kept on using nebulized salbutamol when needed. During elementary school, she has been always described to be overactive with frequent risk-taking behaviours like crossing the street carelessly paying no attention to vehicles. As getting older, she, more often than not, was noticed to be day-dreaming. Her mother always criticised her for being messy, forgetful and loser. She was markedly below par regarding academic tasks at school. She keeps only little company that can withstand her

moodiness. Teachers always denigrate her teasing peers, being noisy in classroom, arguing too much and above all opinionated. Remedial teaching was not that helpful. Apart from her eldest brother, who is maintained on sertraline for recurrent unipolar non-psychotic major depressive disorder, there is no family of neuropsychiatric disorders. She had her menarche at age of [11], and, now menses are regular. No history of illicit drug use. No history of head trauma, epilepsy or toxic exposures. No history of tics. ENT evaluation was non-contributory. She was seen by a private general psychiatrist who prescribed her atomoxetine up to 60 mg for 6 months with mediocre response at best, as reported by patient and parents and consistent with school records. Thyroid function tests were within normal as were iron studies. EEG was done, to exclude remote possibility of complex partial seizures, and deemed normal. Psychometry using Vanderbilt Assessment Scales for ADHD were contemplated, both Parents and Teacher Versions [10], and confirmed ADHD-IA, severe type (8/9 for inattentiveness subscale) with comorbid ODD (6/8 for oppositionality subset). IQ measured using Wechsler Intelligence Scale for children-Third Edition (WISC-III) read 86.

After discussing with parents, a trial with methylphenidate was agreed upon. ECG was normal. Anthropometry recorded at baseline. Weight of 35 kg. Over a week, some tangible improvement was appreciated both at home and school. Methylphenidate, in the form of immediate release Ritalin[®], was titrated up to 30 mg on three divided doses over 2 weeks. For convenience, she was shifted to the long-acting Concerta 36 mg as single morning dose. Response plateaued, rated as

fair by parents but the patient still exhibits scholastic underachievement, albeit better behavioural facets. Concerta was escalated to 54 mg with no ostensibly added benefits. At this point, she had problem sleeping most of nights culminating in erratic school attendance in the morning. Moreover, repeatedly reported by parents was too much anxiety by the patient concomitant with meds. Parents were offered an option of adding clonidine, but they declined it for cardiovascular concerns despite clarification. A trial of augmenting Concerta with agomelatine (Valdoxan[®]) was suggested and fully explained to parents and they consented it and the patient's assent was obtained beforehand. Baseline liver function tests were requested and shown to be within normal lab reference range. Valdoxan 25 mg was added at bedtime with Concerta 54 mg in the morning. Two weeks later, reports were very reassuring, patient could maintain sound sleep and overall scholastic performance was strikingly much better. After another two weeks, marked reduction of anxiety was noted by parents, reported by patient and objectified on Hamilton Anxiety Rating Scale (HAM-A) (scored at 16 compared to baseline score of 27). She is now three months later since the introduction of valdoxan and keeping faring very well. Periodic follow-up of liver function tests was pursued as recommended and was perfectly normal (ALT 12 IU/ml).

Vanderbilt was readministered and documented much lower scores (1/9 for inattentiveness subscale and 3/6 for oppositionality and better DSST scores subsets) going hand-in-hand with the obvious clinical and academic accomplishments Medication chart is portrayed in the table below (Table 1).

Drug Trial	Dose	Duration	Reason To Continue/Discontinue
Strattera	60 mg/d	6 months	Stopped Mediocre Response (IA)
Ritalin (IR)	30 mg/d	2 weeks	Tangible, yet less-than-optimal, response Insomnia and Anxiety Shifted to ER
Concerta	54 mg/d	4 months	For convenience of OD dosing Insomnia and Anxiety Less-than-optimal cognitive response
Valdoxan	25 mg/d	3 months	Sound sleep Serenity Better academic achievement

Table 1: Medication Chart

Discussion

Attention deficit Hyperactivity disorder is one of the most common psychiatric disorders amongst children and adolescents, with approximately 5% of children under 18 years affected worldwide [4]. ADHD is characterized by symptom clusters of inattention, hyperactivity and/or impulsivity. By definition, onset of symptoms must be early in childhood, before age of 12, and differ from what is expected in normal development [11]. Children with ADHD often suffer from other comorbid psychiatric conditions; oppositional defiant disorder, anxiety disorders, conduct disorders and depression are among the most frequent [12].

Growing body of evidence indicates that ADHD is a chronic disorder and that symptoms often persist into adult life. A review by Faraone et al. [13] found a persistency of 15% for young-adults when presence of the full syndrome is considered, and 40-60% when cases in partial remission are included. ADHD is pervasive in the sense that it interferes with multiple domains of functioning, such as at home, in social gatherings and school as well; treatment should seek to improve functioning in all these areas. Multimodal interventions with different treatment targets are theoretically optimal versus pharmacotherapy alone [14]. Close monitoring of treatment response is essential and should include reports from different sources, including parents', patients' and teachers' reports of perceived changes following interventions [5].

Literature is consistent on the effectiveness of stimulant medications and behavioral interventions in the management of the core symptoms of ADHD [6]. Efficacy and safety of these drugs have been extensively examined in numerous clinical trials as well as in systematic reviews and meta-analyses [15-20]. Trials consistently show that stimulants are more effective than placebo, with effect-sizes varying from 0.8 to 1.1 and a positive early clinical response in approximately 70% of cases targeting the neurochemical deficit of catecholamines; dopamine and norepinephrine underlying ADHD.

Most commonly used stimulants are either methylphenidate-based or amphetamine-based. No conclusive evidence exists favoring any of the stimulants over others in terms of efficacy and side effect profile, although current practice seems more in favor of methylphenidate. Most common side effects associated with psychostimulants are insomnia, headache, irritability, agitation, nervousness, tremor, loss of appetite, nausea and weight loss. These unwanted effects tend to be mild, dose dependent and transitory but sometimes dose-limiting and cannot be tolerated [7]. Patients with less than satisfactory response to one stimulant, should undergo a trial of another stimulant category with better outcome [8].

In our case here, due to locally non-availability of stimulants apart from methylphenidate-based, we did not have the luxury to offer an amphetamine-based stimulant for a more robust cognitive response. Dyssomnia in children with ADHD has been emphasized [21], apart from stimulant-induced insomnia. Such insomnia could be tackled pharmacologically, inter alia, by clonidine [22], Melatonin [23], mirtazapine [24] or cyproheptadine [25] or tricyclic antidepressants [26]. In this case, we offered clonidine to cover insomnia, anxiety and inattentiveness issues through alpha-2 agonistic activity. Role of clonidine in alleviating anxiety is well established [27]. In ADHD, long-acting formulation (Kapvay[®]) is FDA-approved.

Unfortunately, this option was declined on the parents' part due to concern about cardiovascular morbidity and mortality of stimulant-clonidine combination [28] despite clarifications. Mirtazapine and, to a lesser extent, cyproheptadine would have been reasonable alternatives for both insomnia and anxiety but due to antihistaminic and antimuscarinic effects, could be counter-intuitive in treating those with attentional impairments. Tricyclic antidepressants have fallen into disfavor, notably, in pediatric population for safety concerns, especially cardiovascular adversity [29].

Melatonin is a safer option that would help insomnia but not anxiety or inattentiveness, especially, treatment-emergent anxiety has been noticed with melatonin. Recently, role of melatonergic receptors M2 in sleep and anxiety was elucidated [30]. Agomelatine, is a novel antidepressant with unique mechanism of action [9]; M1 and M2 agonist with 5HT_{2c} antagonism.

5HT_{2c} antagonism would translate into NE and DA disinhibition [31], consequently the use of agomelatine for ADHD, in theory, seems appealing, albeit off-label and not approved as antidepressant for below age of 18. Niederhofer [32] found agomelatine useful in ADHD. We have the parents consented before embarking on trial after detailed psychoeducation. Response was very impressive as regards the cognitive facets as self-reported by patient, parents and school records and objectified by Digit Symbol Substitution Test (DSST). School reports are both crucial and reliable for monitoring treatment effectiveness [33].

Readministering of Vanderbilt scale documented this improvement (8/9 down to 1/9 for inattentiveness subscales) and using such scales

pre- and post-treatment is advised in clinical setting to quantify symptomatic and functional improvement, despite some limitations, especially, as regards sensitivity to change in response to treatment. Sleep problems were addressed by agomelatine. Anxiety scores markedly diminished on HAM-A (read 16) and clinically. Improvement of sleep quality in context of ADHD cannot explain solely cognitive improvement [34].

Conclusion

We could opine that agomelatine looks an attractive option mitigating stimulant-induced insomnia and anxiety and meanwhile augmenting stimulant response of ADHD core symptoms.

Disclosures

Authors declare no conflicts of interest, nor financial affiliations with pharmaceutical companies or industry-sponsored research.

References

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry* 164: 942-948.
2. Childress AC, Sallee FR (2014) Attention-deficit/hyperactivity disorder with inadequate response to stimulants: approaches to management. *CNS Drugs* 28: 121-129.
3. Reddy DS (2013) Current pharmacotherapy of attention deficit hyperactivity disorder. *Drugs Today (Barc)* 49: 647-665.
4. Stockl KM, Hughes TE, Jarrar MA, Secnik K, Perwien AR (2003) Physician perceptions of the use of medications for attention deficit hyperactivity disorder. *J Manag Care Pharm* 9: 416-423.
5. Pliszka S (2007) AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 46: 894-921.
6. Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, et al. (2011) ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 128: 1007-1022.
7. Mohammadi M, Akhondzadeh S (2011) Advances and considerations in attention-deficit/hyperactivity disorder pharmacotherapy. *Acta Med Iran* 49: 487-498.
8. Budur K, Mathews M, Adetunji B, Mathews M, Mahmud J (2005) Non-stimulant treatment for attention deficit hyperactivity disorder. *Psychiatry (Edgmont)* 2: 44-48.
9. Eser D, Baghai TC, Möller HJ (2010) Agomelatine: The evidence for its place in the treatment of depression. *Core Evid* 4: 171-179.
10. Vanderbilt Assessment Scales (2013) NICHQ, American Academy of Pediatrics, McNeil, 2002 American Psychiatric Association.
11. Meredith SE, Juliano LM, Hughes JR, Griffiths RR (2013) Caffeine Use Disorder: A Comprehensive Review and Research Agenda. *J Caffeine Res* 3: 114-130.
12. Souza I, Pinheiro MA, Denardin D, Mattos P, Rohde LA (2004) Attention-deficit/hyperactivity disorder and comorbidity in Brazil: comparisons between two referred samples. *Eur Child Adolesc Psychiatry* 13: 243-248.
13. Faraone SV, Biederman J, Mick E (2006) The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 36: 159-165.
14. Abikoff H, Hechtman L, Klein RG (2004) Symptomatic improvement in children with ADHD treated with long-term methylphenidate and

- multimodal psychosocial treatment. *J Am Acad Child Adolesc Psychiatry* 43: 802-811.
15. Swanson JM, Elliott GR, Greenhill LL, Wigal T, Arnold LE, et al. (2007) Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. *J Am Acad Child Adolesc Psychiatry* 46: 1015-1027.
 16. Biederman J, Spencer TJ (2008) Psychopharmacological interventions. *Child Adolesc Psychiatr Clin N Am* 17: 439-458.
 17. Adler LA, Newcorn JH (2007) The impact, identification, and management of attention-deficit/hyperactivity disorder in adults. *Introduction. CNS Spectr* 12: 1-2.
 18. Adler LA (2008) Diagnosing and treating adult ADHD and comorbid conditions. *J Clin Psychiatry* 69: e31.
 19. Faraone SV, Buitelaar J (2010) Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *Eur Child Adolesc Psychiatry* 19: 353-364.
 20. Faraone SV, Glatt SJ (2010) A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *J Clin Psychiatry* 71: 754-763.
 21. Bullock GL, Schall U (2005) Dyssomnia in children diagnosed with attention deficit hyperactivity disorder: a critical review. *Aust N Z J Psychiatry* 39: 373-377.
 22. Price JB, Wilens TE, Biederman J (1996) Clonidine for Sleep Disturbances Associated with Attention-Deficit Hyperactivity Disorder: A Systematic Chart Review of 62 Cases. *Am Acad Child Adolesc Psychiatry* 35: 599-605.
 23. Weiss MD, Wasdell MB, Bomben MM, Rea KJ, Freeman RD (2006) Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. *J Am Acad Child Adolesc Psychiatry* 45: 512-519.
 24. Coskun M, Ahmetoglu E, Ozturk M (2010) Mirtazapine treatment for comorbid anxiety/depressive disorders in young subjects with Attention-deficit hyperactivity disorder. *Bulletin of Clinical Psychopharmacology* 20: 3.
 25. Daviss WB, Scott J (2004) A chart review of cyproheptadine for stimulant-induced weight loss. *J Child Adolesc Psychopharmacol* 14: 65-73.
 26. Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Johnstone SJ (2008) Effects of imipramine hydrochloride on the EEG of children with Attention-Deficit/Hyperactivity Disorder who are non-responsive to stimulants. *Int J Psychophysiol* 68: 186-192.
 27. Hoehn-Saric R, Merchant AF, Keyser ML, Smith VK (1981) Effects of clonidine on anxiety disorders. *Arch Gen Psychiatry* 38: 1278-1282.
 28. Popper CW (1995) Combining methylphenidate and clonidine: pharmacologic questions and news reports about sudden death. *J Child Adolesc Psychopharmacol* 5: 157-166.
 29. Amitai Y, Frischer H (2006) Excess fatality from desipramine in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 45: 54-60.
 30. Comai S, Ochoa-Sanchez R, Gobbi G (2013) Sleep-wake characterization of double MT₁/MT₂, receptor knockout mice and comparison with MT₁, and MT₂, receptor knockout mice. *Behav Brain Res* 243: 231-238.
 31. Stahl SM (2014) Mechanism of action of agomelatine: a novel antidepressant exploiting synergy between monoaminergic and melatonergic properties. *CNS Spectr* 19: 207-212.
 32. Niederhofer H (2012) Treating ADHD with agomelatine. *J Atten Disord* 16: 346-348.
 33. Brock SE, Jimerson SR, Hansen RL (2009) Identifying, assessing and treating ADHD at school. Springer US.
 34. Van der Heijden KB, Smits MG, Van Someren EJ, Ridderinkhof KR, Gunning WB (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry* 46: 233-241.