BRIEF COMMUNICATION

Returning to Stimulants in Children with Treatment Resistant ADHD: A Case Series

John D. McLennan MD, PhD[1]; Sterling Sparshu MD[2]

Abstract

Objective: To present a case series of children retrialed on stimulants after initial poor stimulant responses given the paucity of information on the usefulness of this strategy. **Methods:** Health records from an ADHD medication service were obtained for six children who: (i) were medication naïve at service entry; (ii) had trials of at least one stimulant from each stimulant class; (iii) subsequently received a non-stimulant ADHD medication; and, (iv) were then retried on stimulants. **Results:** Initial stimulant discontinuation was a function of adverse effects and/or limited symptom improvement. Minimal response and/or adverse effects to non-stimulants contributed to the decision to retry stimulants. Final ADHD symptom ratings by parents and teachers were significantly better than baseline for this cohort. Three were discharged on stimulants, two as monotherapy. **Conclusion:** Further study is required to develop evidence-based treatment algorithms for treatment resistant ADHD. Retrying a stimulant may be one option.

Key Words: *ADHD, treatment resistant, stimulants*

Résumé

Objectif: Présenter une série de cas d'enfants chez qui on a refait un essai de stimulants après de mauvaises réponses initiales à un stimulant étant donné le peu d'information sur l'utilité de cette stratégie. **Méthodes:** Les dossiers de santé d'un service de médication du trouble de déficit de l'attention avec hyperactivité (TDAH) ont été obtenus pour 6 enfants qui: (i) étaient naïfs au médicament à l'entrée dans le service; (ii) ont eu des essais d'au moins un stimulant de chaque classe de stimulants; (iii) ont subséquemment reçu un médicament non stimulant du TDAH; et (iv) ont ensuite eu un nouvel essai de stimulants. **Résultats:** L'interruption du stimulant initial était en fonction des effets indésirables et/ou de l'amélioration limitée des symptômes. La réponse minimale et/ou les effets indésirables des non-stimulants ont contribué à la décision de ressayer les stimulants. Les évaluations finales des symptômes du TDAH par les parents et les enseignants étaient significativement meilleures qu'au départ pour cette cohorte. Trois ont eu leur congé avec des stimulants, deux avec une monothérapie. **Conclusion:** Il faut plus d'études pour développer des algorithmes de traitement basés sur des données probantes pour le TDAH résistant au traitement. Ressayer un stimulant peut être une option.

Mots clés: *TDAH, résistant au traitement, stimulants*

[1]Children's Hospital of Eastern Ontario-Research Institute; Department of Psychiatry, University of Ottawa; Department of Pediatrics, University of Calgary

[2]Department of Psychiatry, University of Calgary

Corresponding E-Mail: jmclennan@cheo.on.ca

Introduction

When a clinical decision is made to include medication as part of a child's attention-deficit/hyperactivity disorder (ADHD) treatment, stimulants are the first line in most practice guidelines (Seixas, Weiss & Muller, 2012). If an initial stimulant trial is unsuccessful (i.e., insufficient response and/or not tolerated), trying a stimulant from the other class is recommended (i.e., if started with a methylphenidate product, move to an amphetamine-based product, or vice versa) (Wolraich et al., 2011). If stimulant trials from both classes are not adequate and/or tolerated, then typically an approved non-stimulant medication is considered. In Canada, two non-stimulants are approved for children with ADHD: atomoxetine and guanfacine XR.

There is, as of yet, no clear consensus as to what the order of medication choice should be for children with ADHD who have not had an initial acceptable response after being trialed on stimulant from both classes. One explicit operationalized staged approach was put forward by the Texas Children's Medication Algorithm Project (CMAP). In the revised version of CMAP, the following order was proposed in the case of two stimulant class failures: atomoxetine, then certain antidepressants, and then alpha-2-adrenergic agonists (Pliszka et al., 2006). The CMAP authors acknowledged disagreement within their consensus panel as to the position of alpha-2-adrenergic agonists (Pliszka et al., 2000). In addition, their process pre-dated the randomized controlled trial evidence for guanfacine XR and clonidine XR.

In addition to the lack of consensus on the recommended order of ADHD medication, there is a dearth of information on actual sequencing of medication use within clinical practice. While there are important pharmaco-epidemiological studies, these typically consider cross-sectional or collapsed time periods which do not allow determination of medication sequencing (Zetterqvist, Asherson, Halldner, Langstrom, & Larsson, 2013; Beau-Lejdstrom, Douglas, Evans, & Smeeth, 2016). There are, however, at least two exceptions for which detailed medication sequencing in clinical practices were described. The first was a study within community mental health centers in Texas following explicit training in CMAP guidelines (Pliszka et al., 2003). A pattern of retrying stimulant medications after the failure of a non-stimulant was identified rather than following the guideline recommended to continue trying different non-stimulant medications (Pliszka et al., 2003). A second study similarly found a pattern of retrying stimulants after some limited use of non-stimulant medication, rather than exhausting non-stimulant medication options (Wagner, Vallerand, & McLennan, 2014). However, detailed examination of these practice patterns was not provided.

The aims of this study included determining, among a group of children with ADHD who were retried on stimulant medication, (i) the clinical reasoning for (a) discontinuing initial stimulant trials, (b) discontinuing subsequent non-stimulant medication, (c) retrying stimulants, and (ii) the final clinical outcomes.

Methods

Setting: The sample was drawn from the Child Development-Medication Assessment Service (CD-MAS), an outpatient clinic at a public children's hospital in Canada which focused on the pharmacologic management of ADHD. Most children in the clinic, and all within this study, were referred to the service from a school mental health outreach program called Community Outreach of Pediatrics & Psychiatry in Education (COPE) (McLennan, Reckord, & Clarke, 2008).

Sample: The following inclusion criteria were applied to all children treated within CD-MAS between September 1, 2015 and June 30, 2016: (i) the child was medication naïve at time of entry into the service; and, (ii) the child had a trial of at least one methylphenidate-based product, one amphetamine-based product, and one approved non-stimulant ADHD medication before retrying a stimulant medication.

Measures: Data were extracted from health records. CD-MAS used a structured template to document each clinical appointment. This included clear documentation with regard to all medication changes and a section documenting clinical reasoning for medication changes. Additional data available included the child's BMI for each on-site appointment and teacher and parent ratings of ADHD symptom severity. ADHD symptoms were measured by the ADHD symptom section of the MTA-SNAP-IV (Swanson et al., 2001). A modified scoring approach was used resulting in a score ranging from 0-18 with 0 indicating no symptoms rated above "just a little" and 18 indicating that all ADHD symptoms were rated as "very much"(Wagner & McLennan, 2015). Scores at baseline and discharge were extracted and reported.

Analysis: Descriptive statistics were used to summarize treatment receipt and outcomes. Paired t-tests were used to contrast baseline parent and teacher ADHD ratings, as well as differences between baseline and discharge scores by parents and teachers. A p value < 0.05 was set as a threshold for significance. The software program SPSS was used for statistical analysis.

Results

Of 45 children treated in CD-MAS within the study time period, seven met inclusion criteria and parental consent was received for six. Descriptors of the six are summarized in Table 1. As per the inclusion criteria, all children initially were tried on stimulants. While not a requirement, all six were initially started on a methylphenidate medication. All six were also tried on lisdexamfetamine, with four having also been tried on dextroamphetamine-IR. From the approved non-stimulant ADHD medication options, all were

Table 1. Summary of the clinical details of the study sample of children							
Descriptor	1	2	3	4	5	6	Mean (S.D.)
Child sex	Male	Male	Male	Male	Male	Male	--
Child age (years)[a]	7.4	8.8	6.8	8.8	7.3	7.3	7.7 (0.9)
Time in service (years)	4.3	4.0	4.7	3.1	4.6	2.3	3.7 (1.0)
Baseline ADHD rating (parent)[c]	4.5	4.5b	8.5	5.5	5.0b	9.0	6.2 (2.0)
Endpoint ADHD rating (parent)[d]	0.0	0.0	0.0	8.5	0.5	0.0	1.5 (3.4)
Baseline ADHD rating (teacher)	8.5	14.0	12.5	10.0	17.0	15.0	12.8 (3.2)
Endpoint ADHD rating (teacher)[e]	5.0	1.5	1.0	1.0	1.5	1.0	1.8 (1.6)
Baseline BMI (percentile)	32	92	25	25	76	27	46 (30)
Endpoint BMI (percentile)	39	63	16	32	88	22	43 (27)
Number of different medications classes tried	4	5	4	4	4	5	4.3 (0.5)
Number of different medications formulations tried	5	7	5	4	6	6	5.5 (1.0)
Discharged on stimulant[f]	Yes	No	No	Yes	Yes	No	---------

a-At service enrollment

b-Baseline value was missing. First available value is used but child was already on low dose stimulant. Actual baseline ADHD severity may have been higher

c-difference in teacher-parent baseline ratings: t=4.89, df=5, p<0.01; 95% confidence interval (3.2, 10.2)

d-pre-post change in parent ratings: t=2.67, df=5, p<0.05; 95% confidence interval (0.2, 9.2)

e-pre-post change in teacher ratings: t=6.28, df=5, p<0.005; 95% confidence interval (6.5, 15.5)

f-Medication Sequence (with range of total daily dose tried in parentheses)

MPH=Methylphenidate; LDX=Lisdexamfetamine; ATM=Atomoxetine; GXR=guanfacine extended release; DA=dextroamphetamine; IR=immediate release; CR=controlled release; OROS=osmotic release oral system

Case 1: (i) MPH-CR (10-40mg); (ii) LDX (20-30mg); (iii) LDX (30mg) + ATM (0.4-1.1mg/kg); (iv) MPH-CR (20-40mg); (v) ATM (0.7-1.4mg/kg); (vi) GXR (1-3mg); (vii) LDX (20-50mg) + GXR (3mg); (viii) GXR (3mg); (ix) LDX (30-40mg) + GXR (1-3mg); (x) DA-IR (10-20mg) + GXR (1-2mg); Discharge medications: DA-IR (20mg) + GXR (2mg)

Case 2: (i) MPH-OROS (18-36mg); (ii) MPH-IR (40-50mg); (iii) LDX (20-30mg); (iv) MPH-OROS (18mg); (v) ATM (0.6-1.6mg/kg); (vi) Bupropion SR (100-200mg); (vii) Bupropion XL (300mg); (viii) MPH-IR (5-15mg); (ix) GXR (1-3mg); (x) ATM (0.4-1.5mg/kg); Discharge medication: ATM (1.1mg/kg)

Case 3: (i) MPH-CR (20-40mg); (ii) LDX (20-40mg); (iii) LDX (40mg) + DA-IR (2.5-5mg); (iv) ATM (0.42mg/kg); (v) LDX (30-40mg) + ATM (0.43-1.6mg/kg); (vi) LDX (30-50mg) + Risperidone (0.25-1.0mg); (vii) LDX (30-40mg) + Risperidone (0.5-1.0mg) + DA-IR (2.5-5.0mg); (viii) LDX (30mg) + DA-IR (2.5mg); (ix) LDX (20mg); (x) LDX (20mg) + Risperidone (0.25-0.5mg); (xi): LDX (20mg); Discharge medication: None

Case 4: (i): MPH-CR (10-50mg); (ii) LDX (20-40mg); (iii) ATM (0.38-0.68mg/kg); (iv) MPH-CR (10-50mg); (v) GXR (1mg); (vi) MPH-CR (20-40mg); Discharge medication: MPH-CR (30mg)

Case 5: (i): MPH-CR (10-20mg); (ii) LDX (20mg); (iii) ATM (0.3-1.5mg/kg); (iv) Bupropion SR (100-200mg); (v) DA-IR (5mg); (vi) MPH-CR (10-20mg); (vii) MPH-IR (20mg); (viii) DA-IR (5-10mg); (ix) MPH-IR (20-40mg) Discharge medication: MPH-IR (20mg)

Case 6: (i) MPH-CR (10-40mg), (ii) Fluoxetine (5-10mg), (iii) Fluoxetine (10mg) + DA-IR (2.5mg); (iv) Fluoxetine (10mg) + LDX (20-30mg); (v) LDX (30mg); (vi) Atomoxetine (0.4-1.1 mg/kg); (vii) GXR (1-2mg); (viii) ATM (0.4-0.7mg/kg); (ix) DA-IR (2.5-7.5mg); (x) ATM (0.6-1.3mg/kg); Discharged medication: ATM (0.9mg/kg)

tried on atomoxetine and four were additionally tried on guanfacine XR. For off-label medication use targeting attention and/or disruptive behaviors, two were tried on bupropion and one on risperidone. A fluoxetine trial was used for one child targeting comorbid selective mutism. Stimulants were the final discharge medication for three children, two as monotherapy.

ADHD symptom severity at baseline was rated significantly higher by teachers than parents (see Table 1). All children had a reduction in their ADHD symptoms as rated by parents and teachers from baseline to discharge except for one parent. The group's overall ADHD symptom severity scores were significantly lower at discharge as rated by both teachers and parents.

Documented reasoning for medication changes are summarized in Table 2. Adverse effects from stimulants were a factor in discontinuing stimulants for all six children and may have limited the ability to titrate up to maximum recommended doses. Weight loss and/or gastrointestinal complaints were the most common group of adverse effects

Table 2. Summary of medication change rationales across the six cases	
Change type	Reason (case #a)
Discontinuation of stimulant	Adverse effects
	Weight loss/GI complaints (1,1,2,3,3,3,4,4,5,6,6)
	Irritability/sadness (3,4,4,5,5,5,6,6)
	Insomnia (2,5,5,6)
	Tics (2,2)
	Headaches (5)
	Response pattern
	No or minimal improvement (2,2,4,4,5,5)
	Partial response but higher dose not tolerated (1,1,4,6)
	Gains not maintained/developed tolerance(1,1)
	Other
	Parent preference (1,2,5)
Discontinuation of atomoxetine	Adverse effects
	Emotionality/agitation (4,6)
	Weight loss/GI complaints (6)
	Response pattern
	No or minimal improvement (1,1,2,3,5)
Discontinuation of alpha 2 adrenergic agonists	Adverse effects
	Postural hypotension (6)
	Sedation (4)
	Response pattern
	No or minimal improvement (2,4)
	Other
	Unclear if benefiting due to combination therapy (1)
Discontinuation of bupropion	Response pattern
	No or minimal improvement (2,5)
Retrying stimulants	Previous partial response (1,1,3,4,4,6)
	Trying stimulant formulation not previously tried (2,5)
a-case # repeats indicate the effect/issue/rationale arose in more than one medication trial	

contributing to discontinuation. Problems with mood (irritability/sadness) and insomnia were also noted as influencing factors in three or more cases. An inadequate initial response pattern to stimulants was also a factor for the majority of children.

No or minimal improvement was a frequent conclusion from the atomoxetine trials for this cohort leading to discontinuation of this medication, with a minority discontinuing due to adverse effects. Lack of response and adverse effects were also an issue for guanfacine XR. The two main reasons documented for retrying stimulants were that a previous partial response had occurred with a stimulant and that a different stimulant formulation was to be tried.

Case 1: This boy had an initial robust response to stimulants that quickly faded and was not recaptured despite dose increases. Higher stimulant titrations were not tolerated

given excessive weight loss (pre-treatment BMI dropped quickly from the 32nd to 12th percentile). During subsequent treatment, there was marked variability in reported response to medications over time and across informants making it difficult to tease out optimal medication dosing. This boy was also tried on atomoxetine and guanfacine XR monotherapy, as well as medication combinations. It was finally judged that a combination of low-dose lisdexamfetamine and guanfacine XR resulted in the best response and tolerability. However, lisdexamfetamine was subsequently replaced by dextroamphetamine IR given a marked lag in the onset of action from lisdexamfetamine resulting in substantial morning struggles in school which appeared to be better addressed by dextroamphetamine IR dosing.

Case 2: This boy had an initial transient positive response to stimulants that was not subsequently recaptured with dose increases or with additional stimulant trials. He also

experienced tic exacerbation that appeared related to stimulants. During the first atomoxetine trial, there was inconsistent feedback as to whether atomoxetine was helpful. This may have been in part due to a classroom placement that was not a good fit for his combined learning disability and ADHD. Neither guanfacine XR nor bupropion were effective. A repeat of the atomoxetine trial, when the student was in a specialized classroom placement for children with learning disabilities, was found to result in a substantial ADHD improvement.

Case 3: This boy initially had modest responses to stimulants. However, chronic poor appetite and poor weight gain/weight loss were substantial. This lead to a brief trial of atomoxetine monotherapy, but he significantly deteriorated off of stimulants with return of his aggressive behavior. He was started back on a moderate stimulant dose and a more complete atomoxetine trial was conducted. No gains were evident from the atomoxetine. Stimulants alone did not appear adequate and aggression persisted despite specialized classroom placement. Higher doses of stimulants were not possible due to poor weight gain/weight loss. Risperidone was subsequently added. Over time behavior improved substantially, potentially in part due to a new specialized classroom placement. Risperidone was eventually withdrawn. His behavior continued to improve and he was mostly integrated back into typical classroom settings with limited need for specialized support. Given his significant improvement, a trial of stimulant reduction and eventual discontinuation was undertaken. He continued to do well and was eventually discharged on no medication.

Case 4: This boy showed an inconsistent treatment response to initial stimulant trials and had significant weight loss (baseline BMI at 25th percentile dropped to the 4th percentile at one point). On atomoxetine he became restless and more emotional. Low dose guanfacine XR caused substantial sedation. As parents had seen a partial response within initial stimulant trials, it was agreed to retry stimulants. A more robust response was seen at school on this repeat trial. By only giving medication on school days, adequate weight was maintained. Parents found some home behavior challenging but manageable.

Case 5: This boy had a poor initial response to two stimulants and multiple adverse effects including marked insomnia and emotionality. Retrying stimulants using short acting agents also seemed to trigger significant adverse effects. No benefits from non-stimulants were realized. After a break from medication, he returned to the clinic for further medication trials, given his ongoing functionally impairing ADHD symptoms. Moderately dosed, immediate release methylphenidate was tolerated at the re-trial point and was judged to result in a good response. He was discharged on stimulants.

Case 6: This boy demonstrated an inconsistent initial response pattern to stimulants. He did not tolerate higher dose stimulants, which resulted in his BMI dropping from the 27th to the 5th percentile. His course of treatment was complicated by a period of selective mutism that was judged more impairing than his ADHD symptoms at the time and prompted a trial of fluoxetine. After resolution of selective mutism and withdraw of fluoxetine, a more focused effort was undertaken to treat his ADHD symptoms. He appeared to have a partial response to atomoxetine but it did not appear sufficiently robust or consistent, so it was discontinued. Next he was trialed on guanfacine XR but experienced postural hypotension. Around this time he obtained a specialized placement in a supportive mental health classroom. In this new setting some medication trials were repeated and it was determined that a modest, but more detectable, partial response to atomoxetine was realized.

Discussion

Some children with ADHD who have a poor initial response to stimulants may benefit from retrying stimulants at a later point. Presumably retrying stimulants would not be required in a child with ADHD who already completed two stimulant trials, one from both classes, using full dose ranges (when tolerated), and showed no improvements at all and there were not any significant contextual factors that may have compromised treatment delivery or assessment of that treatment. However, these ideal scenarios do not often occur within typical practice. Rather there will likely be a need to consider a number of factors to inform a decision as to whether to return to stimulants including: (i) whether there was any partial response to initial stimulant trials; (ii) the severity of adverse effects to stimulant medications; and, (iii) the impact of various contextual factors.

Attempting to operationalize what is a partial or even full response to ADHD medication is complex. Obtaining an ADHD symptom score of ≤ 1 on the MTA-SNAP-IV using traditional scoring is one operationalization of this goal (Steele, Jensen, & Quinn, 2006). Within the CD-MAS service, a guiding target was ADHD symptom resolution defined as a score of 0 using a modified scoring of the MTA-SNAP-IV which can be consider more stringent than achieving a score of ≤ 1 on the MTA-SNAP-IV using traditional scoring (Wagner & McLennan, 2015). This guided the CD-MAS clinicians' recommendations as to whether to suggest additional medication titration, while simultaneously taking into account any emerging adverse effects and whether maximum recommended dosing had been reached. Parents, and children themselves if they were capable of treatment decisions, could decline any recommended dose increase or medication change.

CD-MAS did not define a partial response threshold. However, parent and teacher ratings were collected prospectively and documented so that the degree of symptom change could be reviewed at a later point. For example, a subsequent response to a non-stimulant could be contrasted

with findings from the original stimulant trials (as well as physiological patterns, e.g., drop in BMI percentile). This approach may have captured partial stimulant responses which may have contributed to decisions to retry stimulants in some children. If such information had not been collected and documented, it is possible that a more categorical judgement may have been made that a stimulant failed and hence a decision not to return to retry stimulants.

Response rates to non-stimulant medications following poor response to both stimulant classes are not systematically known. Randomized controlled trials of non-stimulant medications and estimates of effect sizes often include children who are medication naïve or without documented response patterns to stimulants. This precludes estimates of response rates or effect sizes in the subpopulation of most interest, i.e., those failing two classes of stimulants. A partial exception includes subgroup analysis of a cross-over study which identified that 43% of children who did not respond to methylphenidate-OROS, subsequently responded to atomoxetine (Newcorn et al., 2008). Trials of adjunctive use of guanfacine XR and clonidine XR also provide partial information on response rates in those without adequate response to stimulant monotherapy (Kollins et al., 2011; Wilens et al., 2012). However, more refined data are needed for the clinician to be able to provide more detailed information to decision-makers (e.g. parents) as to the anticipated benefits from pursuing non-stimulant medication options post inadequate response to stimulants.

There are several additional contextual factors that may need to be taken into consideration in deciding whether to retry stimulants. Child age may be one. If a child had initially been tried on stimulants at a young age, especially as a preschooler, and the stimulant was discontinued due to adverse effects, it is possible that a retry at an older age might be better tolerated given that young age may be associated with higher rates of adverse stimulant effects (Wigal et al., 2006). Furthermore, tolerance to adverse effects at a later age may allow stimulant titration to higher doses which may result in more robust responses in some children.

Another potential contextual factor to consider is whether setting influenced the lack of a response. For example, if the first stimulant trial occurred in a classroom placement that was problematic (e.g. inadequate supports for a comorbid mental or learning disorder), a retrial once a child is in a more supportive classroom might allow detection of significant stimulant effects. Similarly, lack of stability of home life during a trial may cloud potential benefits and/or influence medication adherence. Within some of the cases in this study there were examples in which ADHD ratings from the school were not in keeping with qualitative descriptions of change in the child or from other informants. In some cases, robust responses to stimulants (and other medications) were found when the medication was retried and information obtained from a different teacher.

Limitations

This study has several limitations. First, it was based on a very small sample size. Second, the evaluations were in a clinical context and did not include blinding or placebo controls. Given multiple poor responses to medication for this sample, it is suggested that there was not a strong bias towards exaggerating a positive response. Third, there were not external restrictions on the duration or volume of physician-contact per child within the service. This allowed children to be seen over an extended period of time and on a regular basis. This service has been reported to have a mean of 11.6 (SD 9.5) clinical contacts (combination of phone and onsite contacts) per child (Wagner, Vallerand, & McLennan, 2014). This may differ from other clinical settings where there may be more restricted number of mental health visits.

Recommendations

Further studies are required to determine intervention response patterns in children with ADHD who have initial poor response to stimulants. Within such studies, there should be: (i) operationalization as to what constitutes a poor or inadequate medication response; (ii) documentation of potential influencing contextual factors; and, (iii) determination of response pattern on stimulant retrials. Such information would allow for the development of evidence-based guidelines for those who may be considered treatment resistant.

Acknowledgements / Conflicts of Interest

References

Beau-Lejdstrom, R., Douglas, I., Evans, S. J. W., & Smeeth, L. (2016). Latest trends in ADHD drug prescribing patterns in children in the UK: Prevalence, incidence and persistence. *BMJ Open, 6*(6), e010508.

Kollins, S. H., Jain, R., Brams, M., Segal, S., Findling, R. L., Wigal, S. B., & Khayrallah, M. (2011). Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. *Pediatrics, 127*(6), e1406-1413.

McLennan, J. D., Reckord, M., & Clarke, M. (2008). A mental health outreach program for elementary schools. *Journal of the Canadian Academy of Child & Adolescent Psychiatry, 17*(3), 122-130.

Newcorn, J. H., Kratochvil, C. J., Allen, A. J., Casat, C. D., Ruff, D. D., Moore, R. J., & Michelson, D. (2008). Atomoxetine and osmotically released methylphenidate for the Treatment of Attention Deficit Hyperactivity Disorder: Acute Comparison and Differential Response. *American Journal of Psychiatry, 165*(June), 721-730.

Pliszka, S. R., Crismon, M. L., Hughes, C. W., Conners, C. K., Emslie, G. J., Jensen, P. S.,…The Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention-Deficit/Hyperactivity Disorder. (2006). The Texas Children's Medication Algorithm Project: Revision of the Algorithm for Pharmacotherapy of Attention-Deficit/

Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *45*(6), 642-657.

Pliszka, S. R., Greenhill, L. L., Crimson, M. L., Sedillo, A., Carlson, C., Conners, C. K.,…The Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention-Deficit/Hyperactivity Disorder. (2000). The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Attention-Deficit/Hyperactivity Disorder. Part I. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*(7), 908-919.

Pliszka, S. R., Lopez, M., Crismon, M. L., Toprac, M. G., Hughes, C. W., Emslie, G. J., & Boemer, C. (2003). A feasibility study of the children's medication algorithm project (CMAP) algorithm for the treatment of ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*, *42*(3), 279-287.

Seixas, M., Weiss, M., & Muller, U. (2012). Systematic review of national and international guidelines on attention-deficit hyperactivity disorder. *Journal of Psychopharmacology*, *26*(6), 753-765.

Steele, M., Jensen, P. S., & Quinn, D. M. P. (2006). Remission versus response as the goal of therapy in ADHD: A new standard for the field? *Clinical Therapeutics*, *28*(11), 1892-1908.

Swanson, J. M., Kraemer, H. C., Hinshaw, S. P., Arnold, L. E., Conners, C. K., Abikoff, H. B.,…Wu, M. (2001). Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and ODD symptoms at the end of treatment. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(2), 168-179.

Wagner, D. J., & McLennan, J. D. (2015). An Alternative Approach to Scoring the MTA-SNAP-IV to Guide Attention-Deficit/Hyperactivity

Disorder Medication Treatment Titration towards Symptom Remission: A Preliminary Consideration. *Journal of Child & Adolescent Psychopharmacology*, *25*(10), 749-753.

Wagner, D. J., Vallerand, I. A., & Mclennan, J. D. (2014). Treatment Receipt and Outcomes from a Clinic Employing the Attention-Deficit/Hyperactivity Disorder Treatment Guideline of the Children's Medication Algorithm Project. *Journal of Child & Adolescent Psychopharmacology*, *24*(9), 472-480.

Wigal, T., Greenhill, L., Chuang, S., McGough, J., Vitiello, B., Skrobala, A.,…Stehli, A. (2006). Safety and Tolerability of Methylphenidate in Preschool Children With ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*, *45*(11), 1294-1303.

Wilens, T. E., Bukstein, O., Brams, M., Cutler, A. J., Childress, A., Rugino, T.,…Youcha, S. (2012). A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(1), 74-85.e2.

Wolraich, M., Brown, L., Brown, R. T., DuPaul, G. J., Earls, M. F., Feldman, H. M.,…Visser, S. (2011). ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics*, *128*(5), 1007-1022.

Zetterqvist, J., Asherson, P., Halldner, L., Langstrom, N., & Larsson, H. (2013). Stimulant and non-stimulant attention deficit/hyperactivity disorder drug use: Total population study of trends and discontinuation patterns 2006-2009. *Acta Psychiatrica Scandinavica*, *128*(1), 70-77.