Treatment Response and Time to Treatment Discontinuation in Young Children with ADHD: An Analysis of Real-World Data from Electronic Medical Records

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Introduction

- While guidelines recommend behavioral interventions to address symptoms of ADHD in preschool-aged children[1,2], there is widespread use of pharmacological interventions.
- Compared to older children and adults, relatively little is known about the *comparative* effectiveness of different medications in the management of ADHD in preschoolers.
  - The preschool ADHD treatment study demonstrated methylphenidate to be an efficacious treatment in this age group, but did not directly evaluate for the comparative efficacy of alternative agents[3].
  - Recently, the comparative effectiveness and tolerability of alpha2 agonists compared to stimulants was evaluated and revealed stimulants to be significantly more effective, but less tolerable than alpha2 agonists[4].
  - The same study revealed that length of stimulant treatment was significantly longer than alpha 2 agonists for children who initiate stimulants at or after the age of 4[4].
- The current analysis sought to use a large database of de-identified real-world patient data to expand on the Harstad et al analysis evaluating the comparative effectiveness of stimulant and non-stimulant treatments in young children with ADHD.

Methods

Data Source:

The data source for analyses was *NeuroBlu*[5], a commercially available dataset derived from specialty electronic health record data. The overall dataset within NeuroBlu consists of approximately 560,000 de-identified patient records. Data were collected longitudinally over approximately 20 years and from 25 geographically diverse sites in the United States. From this database, de-identified data for 3769 young children with ADHD were analyzed within the NeuroBlu platform.

Inclusion Criteria:

- Received a first ICD 9/10 diagnosis of ADHD prior to the age of 6 years.
- Treated with at least one of the following medications:
  - Stimulant medications: amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, and methylphenidate.
  - Non-stimulant medications: clonidine and atomoxetine.

Exclusion Criteria:

- Did not have CGI-S severity data at index state of medication

Data Processing/Outcomes:

Table 1: Collected variable data pre-processing.

Variable	Processing
Age (at the time of treatment start).	No transformation
Medication	No transformation
Length of Treatment	Treatment end time-treatment start time
Baseline Clinical Global impression of severity (CGI-S) score	Mean of CGI-S scores in the period from 3 months prior to treatment initiation
Post-treatment CGI-S score	Mean of CGI-S scores collected between 3 months and 6 months post-Baseline

Statistical Analysis

- Two separate analysis were conducted:
  - Grouped evaluation of the comparative effectiveness of all stimulant medications as compared to all non-stimulant medications was conducted utilizing 2-tailed independent sample t-tests (2-tailed) comparing cross group differences in Post-Treatment minus Baseline CGI-S scores and in length of treatment (in days)
  - Differences in change in CGI-S scores and in length of treatment across all medication were evaluated using one-way ANOVA
  - Where ANOVA revealed statistically significant differences across medications, Tukey HSD test was used to explore pairwise comparisons

Results

Within group counts, demographic descriptors, and mean(sd) outcome measures are reported in Tables 2 and 3 in addition to Figures 1 and 2.

- Cross-class and cross-medication changes in CGI-S scores were not statistically significant (p=0.071 and 0.387 respectively).
- Cross-class analysis of length of treatment revealed statistically significant differences(p<0.001) with length of treatment of stimulant medications exceeding non-stimulant medications (table 2).
- Cross-medication analysis revealed average lengths of treatment of clonidine to be significantly longer than all other agents except methylphenidate, length of treatment of methylphenidate was significantly longer than all treatments except for clonidine and dexmethylphenidate (Figure 3).

Table 2: Group and medication gender counts and mean age at time of treatment start.

Group	Patient Count (n)	Gender Count (n) Female	Gender Count (n) Male	Age mean(sd)
Full	3769	964	2804	5.91(1.48)
Stimulant	3232	793	2438	6.02(1.53)
Non-stimulant	1472	381	1091	6.44(1.78)
Amphetamine	1155	266	889	6.25(1.83)
Methylphenidate	2115	523	1592	6.29(1.65)
Lisdexamfetamine	887	223	664	6.72(1.9)
Dextroamphetamine	1311	307	1004	6.19(1.78)
Dexmethylphenidate	730	167	562	6.39(1.73)
Clonidine	1069	274	795	6.55(1.89)
Atomoxetine	578	144	434	6.46(1.76)

Table 3: Group and medication mean CGI scores at time of treatment start, at the interval (3-6 months post treatment start) point and length of time on medication.

Group	Start CGI-S mean(SD)	CGI-S Interval Change mean(SD)	Time on Medication (days) mean(SD)
Full	4.32(4.32)	0.15(0.55)	829.15(816.47)
Stimulant	4.29(4.29)	0.16(0.6)	772.41(777.81)
Non-stimulant	4.4(4.4)	0.12(0.62)	623.92(708.3)
Amphetamine	4.3(4.3)	0.17(0.69)	477.81(602.03)
Methylphenidate	4.32(4.32)	0.16(0.61)	599(697.41)
Lisdexamfetamine	4.25(4.25)	0.12(0.69)	511.34(611.21)
Dextroamphetamine	4.29(4.29)	0.18(0.69)	504.09(616.46)
Dexmethylphenidate	4.3(4.3)	0.13(0.64)	525.38(616.42)
Clonidine	4.45(4.45)	0.12(0.59)	646.68(703.49)
Atomoxetine	4.37(4.37)	0.14(0.68)	453.43(630.26)

Figure 1: Difference in CGI-S score between Baseline CGI-S and Post Treatment CGI-S for medication groupings and individual medications.

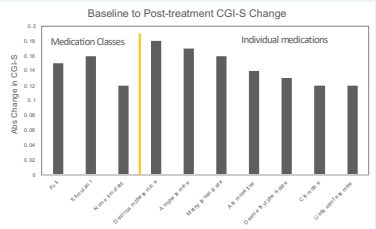


Figure 2: Mean time on medication (in days) for medication groupings and individual medications.

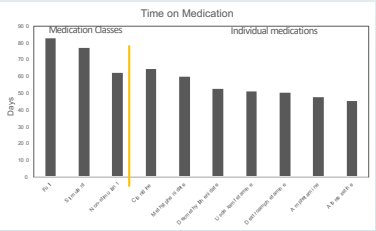
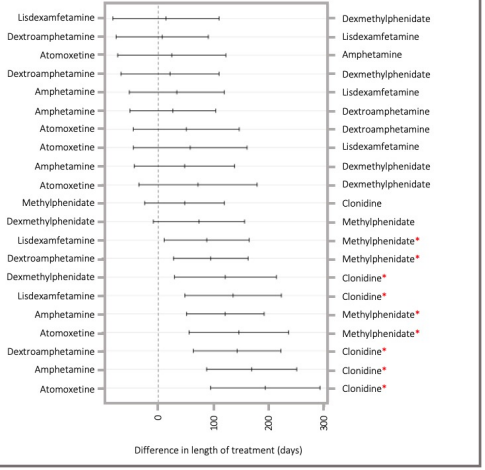


Figure 3: Forest plot of difference in length of treatment between medications.



Conclusion

- No statistically significant differences were revealed in CGI-S change scores across stimulant and non-stimulant medication classes in our cohort of young children with ADHD.
- **Length of treatment was significantly longer for patients receiving stimulant treatment as compared to those receiving non-stimulant medications.**
- Individual medication analysis, however, revealed that length of treatment was significantly longer for clonidine and methylphenidate as compared to nearly all other agents, except for methylphenidate in the case of clonidine and except for dexmethylphenidate and clonidine in the case of methylphenidate.

Limitations

- A subset of patients within the evaluated groups were on a combination of ADHD treatments making definitive determination of individual agent efficacy difficult.
- Our cohort was selected based on having had a diagnosis of ADHD prior to the age of 6, specific treatment start time, however, varied with the average treatment start time being 5.91 years of age.

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Disclosures

- MB is a paid consultant for Holmusk Technologies; SHK is a full-time employee for Holmusk Technologies