Stimulant Dosing Strategy Effects on Treatment Outcomes in Children & Adolescents with ADHD

Based on a 2022 Meta-Analysis by Dr. Luis C. Farhat and Colleagues

Molecular Psychiatry; doi.org/10.1038/s41380-021-01391-9

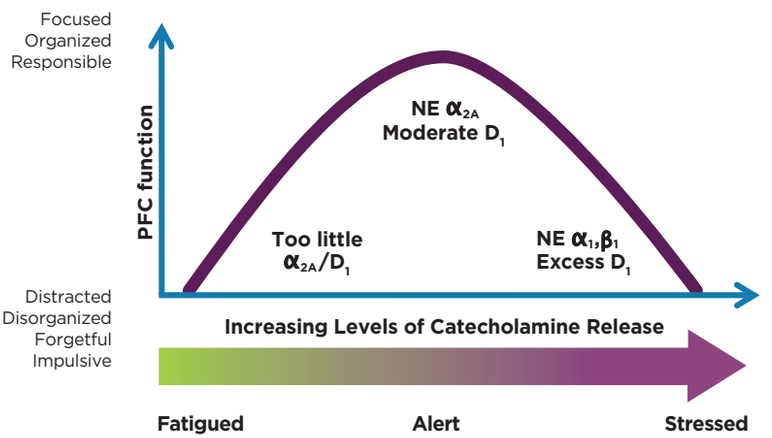
> *Treating ADHD is easy; treating ADHD well takes a lot more skill and effort.*[1]

Dose-Optimization Increases Efficacy and Improves Adherence[2]

- Suboptimal treatment of ADHD occurs when patients are not rigorously titrated; it is therefore important to **dose optimize across the entire FDA-licensed dose range:**
  - Even larger reductions in ADHD symptoms can be achieved if the decision to use higher doses is individualized, considering ADHD symptom severity and dose-limiting adverse events (AEs)
  - Flexible titration mitigates the risks of discontinuing due to AEs
- **Flexible titration as needed and tolerated to higher doses of stimulants is associated with both improved efficacy and acceptability** because practitioners can increase/reduce doses based on control of ADHD symptoms vs. dose-limiting AEs
- **Clear, evidence-based communication with families** about the importance of escalating doses could help decrease their concerns regarding flexible titration to higher doses

The Brain Requires an Optimal Balance of Catecholamines, Dopamine (DA) & Norepinephrine (NE)

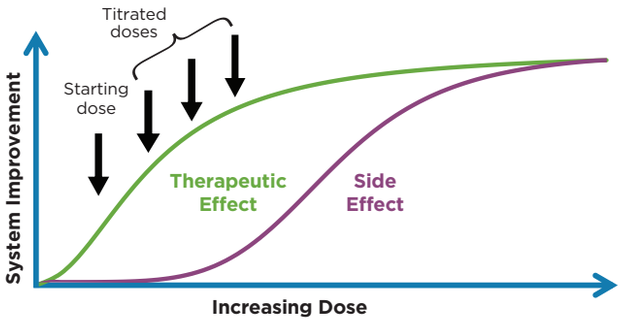
FIGURE 1: PFC is Sensitive to its Neurochemical Environment



- FDA-approved **ADHD medications**, such as stimulants, are thought to **act, in part, through DA and/or NE**[1,3]
- DA and NE are **important modulators** of the key prefrontal cortex (PFC) **brain circuits** that support **attention, reward processing**, and **activity levels**[1,3]
  - **NE stimulation** of α_{2A} receptors strengthens network connectivity (**increases 'signals'**)[3]
  - **Moderate DA** activation of D_1 receptors weakens inappropriate connections (**decreases 'noise'**)[3]
- Both **too little and too much** DA and NE result in **suboptimal cognitive functioning**[3]

Titrate to Achieve the Individual's Optimal Dose

FIGURE 2 – Relationship between Titration and the Dose-Response Curve



- **Start at low doses and titrate up to achieve the optimal dose**[4-5]
- Goal is to achieve **maximum benefit while minimizing AEs**[4]
- Substantial improvement can occur after the first dose tried, **but more improvement is often seen with continued titration**[1]

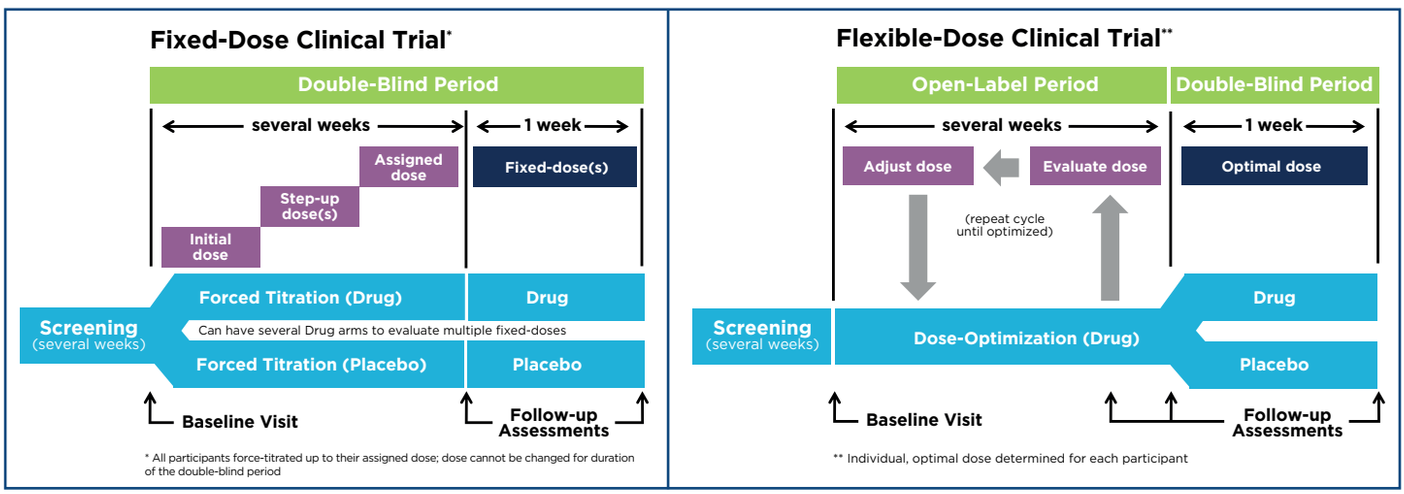
Guidelines & professional organizations recommend titrating to the dose with maximum benefit and least AEs[1, 5-6, 7-10]

Different Clinical Trial Designs Provide Different Clinical Outcomes with Stimulant Dosing[2,11]

Background

- **Fixed-dose trials are important during the drug development process** of new medications to evaluate dose dependency and inform efficacy and safety[2]
- However, if the data from **fixed-dose trials** are applied clinically, they **may lead to suboptimal dosing** or a dose with **intolerable side effects**[11]
- **Flexible-dose trials** are better at mimicking **actual clinical practice** and better reflect risk/benefit considerations since dose may be changed in accordance with **individual patient response**[2,11]

FIGURE 3 – Fixed-Dose vs. Flexible-Dose Clinical Trial Designs



Definitions

Efficacy
change in ADHD symptom severity scores on standardized scales

Tolerability
treatment discontinuation due to adverse events

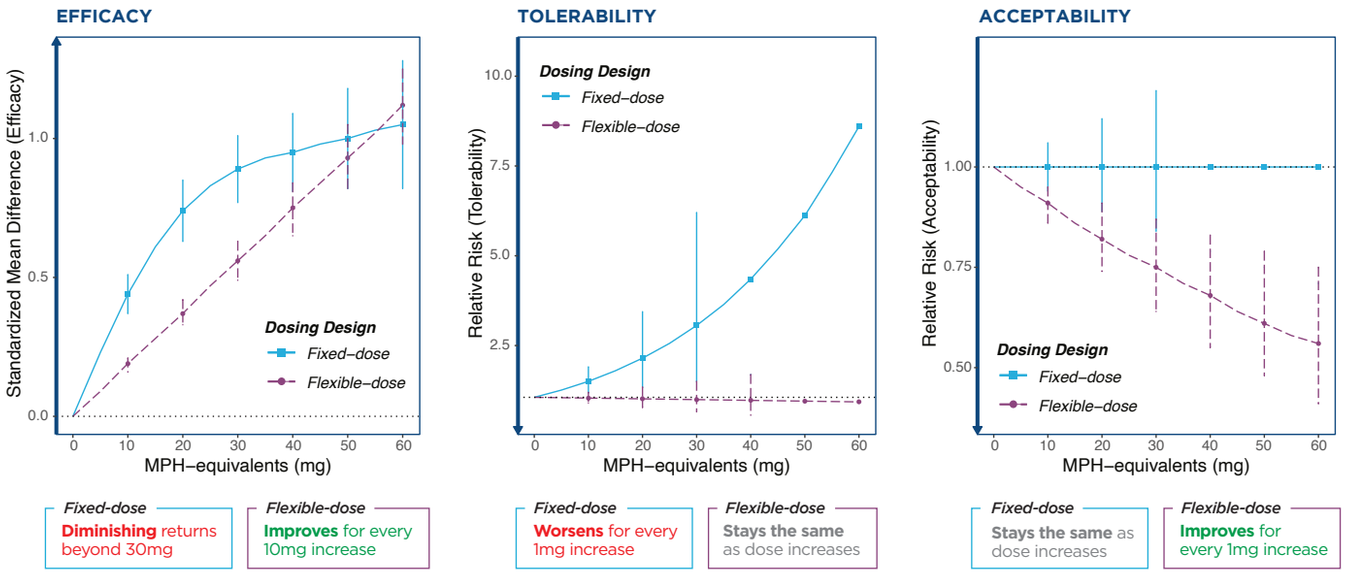
Acceptability
treatment discontinuation for any reason

As dose increases across the FDA-licensed dose range†

Based on a meta-analysis of 65 double-blind, randomized controlled trials of various stimulant formulations against placebo in 7,877 children and adolescents with ADHD, the following conclusions were drawn:[2]

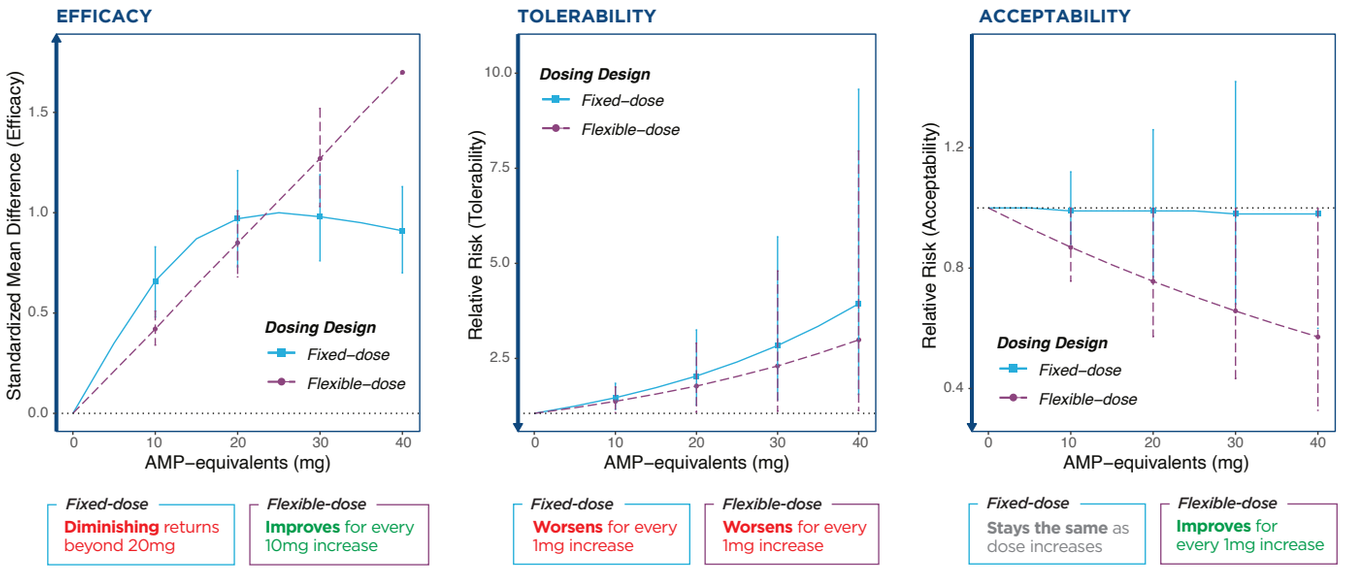
FIGURE 4 – Dose-Response Curves for MPH and AMP

Methylphenidate (MPH)



	Fixed-dose	Flexible-dose
EFFICACY	**Diminishing** returns beyond 30mg	**Improves** for every 10mg increase
TOLERABILITY	**Worsens** for every 1mg increase	**Stays the same** as dose increases
ACCEPTABILITY	**Stays the same** as dose increases	**Improves** for every 1mg increase

Amphetamine (AMP)



	Fixed-dose	Flexible-dose
EFFICACY	**Diminishing** returns beyond 20mg	**Improves** for every 10mg increase
TOLERABILITY	**Worsens** for every 1mg increase	**Worsens** for every 1mg increase
ACCEPTABILITY	**Stays the same** as dose increases	**Improves** for every 1mg increase

The meta-analysis by Dr. Farhat and colleagues, summarized here, provides evidence demonstrating **the importance of dose optimization across the entire FDA-licensed dose range** unless ADHD symptom severity diminishes to the point where there is little room for further improvement, or dose-limiting AEs appear, **in the management of ADHD in children/adolescents**.[2]

† Doses of different MPH and AMP products were converted to MPH- and AMP-equivalent doses, using as reference quantities of d-MPH and d,l-AMP in short-acting MPH hydrochloride and mixed-AMP salts preparations, respectively. Conversions also adjusted for different pharmacokinetics of each medication.

For additional information on this topic, please see our comprehensive, interactive summary:
https://trismedical.com/resources/dosing-int

References

FIGURE 1: Image adapted from, Titration graph (https://commons.wikimedia.org/wiki/File:Titrated_doses.svg) licensed under CC BY-SA 4.0 (https://creativecommons.org/licenses/by-sa/4.0/deed.en).

FIGURE 2: Image adapted from Arnsten A. *CNS Drugs.* 2009;23(Suppl. 1):33-41.

FIGURE 3: Image created by Tris Medical.

FIGURE 4: Image adapted from Farhat LC et al. *Molecular Psychiatry*. 2022:doi.org/10.1038/s41380-021-01391-9.

1. Rohde LA, et al. The World Federation of ADHD Guide. Web 2019 (https://www.adhd-federation.org/_Resources/Persistent/6d9ca34c09972aea00d0ea6d02be6f6d6bd5bb4c/The%20WF%20ADHD%20Guide_072019.pdf).
2. Farhat LC, et al. *Molecular Psychiatry*. 2022:doi.org/10.1038/s41380-021-01391-9.
3. Arnsten A. Toward a new understanding of ADHD pathophysiology. *CNS Drugs.* 2009;23(Suppl. 1):33-41.
4. Maxwell S (2013). "Chapter 2: Therapeutics and Good Prescribing: Choosing a Dosing Regime". In Walker BR, Colledge NR, Ralston SH, Penman ID (eds.). Davidson's Principles and Practice of Medicine. Elsevier Health Sciences. p. 34. ISBN 978-0-7020-5103-6.
5. CADDRA 2018: Canadian ADHD Practice Guidelines Fourth Edition Revised Dec 6 (Final). Web 2018 (https:/www.caddra.ca/wp-content/uploads/CADDRA-Guidelines-4th-Edition_-Feb2018.pdf).
6. Nationwide Children's Hospital and Partners for Kids. Prescribing Guidelines for ADHD. Web 2022 (https://www.nationwidechildrens.org/-/media/nch/for-medical-professionals/practice-tools-new/prescribing-guidelines-for-adhd.ashx).
7. Wolraich ML, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics*. 2019; 144 (4): e20192528.
8. NICE guideline. ADHD: Diagnosis and Management. Web 2018 (http://www.nice.org.uk/guidance/ng87).
9. Pliszka S, et al. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adol Psychiatry*. 2007; 46(7):894-921.
10. Post RE, et al. Diagnosis and management of ADHD in adults. *Am Fam Physician*. 2021;85(9):890-896.
11. Lipkovich I, et al. *BMC Psychiatry*. 2008;8(3):doi:10.1186/1471-244X-8-3.

Abbreviations

AEs	Adverse events	**DA**	Dopamine
α_1	Alpha 1 adrenergic receptor	**D_1**	Dopamine receptor 1
α_{2a}	Alpha 2a adrenergic receptor	**FDA**	Food & Drug Administration
AMP	Amphetamine	**MPH**	Methylphenidate
ADHD	Attention Deficit/Hyperactivity Disorder	**NE**	Norepinephrine
β1	Beta 1 adrenergic receptor	**PFC**	Prefrontal Cortex

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