Tris MEDICAL PHARMA

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

A 2022 Meta-Analysis by Dr. Luis C. Farhat and Colleagues

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

Highlights About the Importance of Dose-Optimization[2]

Dose optimization evidence

The meta-analysis by Dr. Farhat and colleagues 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.**

Suboptimal treatment

Suboptimal treatment of ADHD occurs when patients are not rigorously titrated, thus it is important to **dose optimize across the entire FDA-licensed dose range.**

Flexible titration

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.

Better communication

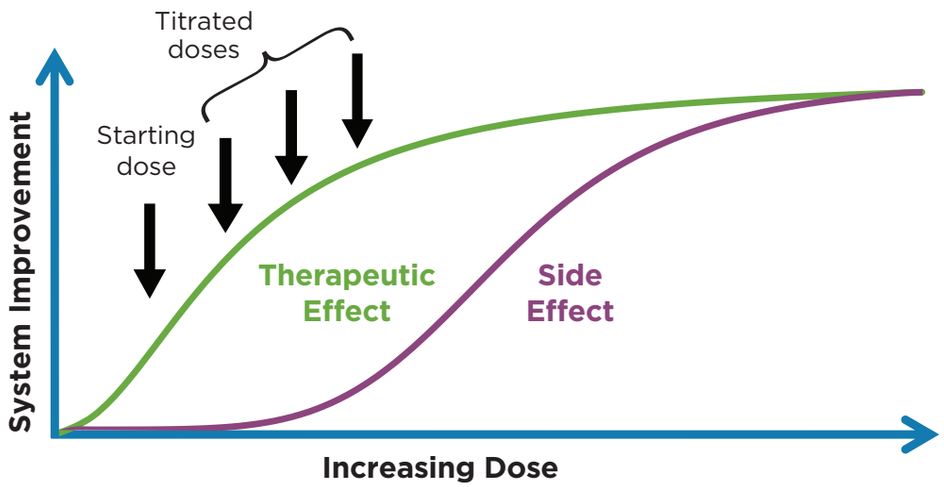
Clear, evidence-based communication with families about the importance of escalating doses could help decrease their concerns regarding flexible titration to higher doses.

Why Titrate?

Overview of Titration

The goal of drug titration is to **adjust the dose of a medication to achieve the optimal dose,** defined as the dose which provides **maximum benefit** while **minimizing adverse effects.**[3]

FIGURE 1 – Relationship between Titration and the Dose-Response Curve



- The key to a successful titration is the **routine use of standardized instruments** to measure treatment response and to also routinely assess for adverse effects.[1]
- For stimulants, it is not possible to predict what the optimal dose will be before starting treatment.[1]
- Therefore, it's **necessary to individually titrate patients onto each new medication** while carefully measuring both their response and any adverse effects.[1]

Thus, **despite current recommendations, children/adolescents often receive relatively small daily dosages of stimulants** in the community in the US, with an average daily dose of ~20–25 mg of methylphenidate and ~20 mg of mixed amphetamine salts which likely **contributes to suboptimal efficacy** in ADHD and non-ADHD domains, **nonadherence** and increasing trends of **polypharmacy**.[2]

Why Can Determining Optimal Dose be Challenging?

- Optimal treatment means that the symptoms have decreased and that there is improvement in general functioning.[4]
- Optimal dose is that dose above which there is no further improvement. Sometimes side effects limit the dose titration.[4]
- However, it is not uncommon for **parents to report that symptoms have been optimized after the initial dose**, because they have been surprised by how much the symptoms have improved, only to realize later that there was **actually still quite a lot of room for improvement**.[1]

Observations about Titration in Clinical Practice

- Prescribing guidelines for stimulant medications **recommend beginning with low starting** doses as well as **titrating up** at specified dose increments and at intervals of once every **3 days to weekly**.[5]
- However, in clinical practice, while roughly 2/3 of children and ½ of adults receive at least 1 dose adjustment within the first year, it's **often almost 3 to 4 months until the first dose adjustment** occurs in either population.[6,7]
- Furthermore, in pediatric patients, **early titration and early physician contact** with parents is related to greater medication supply and **continuity of treatment**.[6,7]
- Unfortunately, psychiatrists have reported that the most common reason for not using a rigorous titration schedule was that **family members declined further dose escalation once some improvement in the child's behavior was observed**.[2]

What do the Guidelines say about Titration?

In addition to what prescribing information recommends, **practitioners are advised to start at low doses and titrate up until symptom remission as tolerated to achieve the individual's optimal dose.[2]**

National

[American Academy Pediatrics (AAP) ADHD Guidelines (2019):](#) The primary care clinician should titrate doses of medication for ADHD to achieve maximum benefit with tolerable side effects.[8]

[World Federation of ADHD Guide (2019):](#) We have tended to increase the dose until there is clearly no improvement between doses and then revert to the lowest dose with the maximum benefit and least adverse effects.[1]

[American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameters for ADHD (2007):](#) After starting a medication, titration upward may occur every 1-3 weeks until the maximum stimulant dose is reached, symptoms of ADHD remit, or SEs prevent further titration, whichever occurs first.[9]

International

[Canadian ADHD Resource Alliance (CADDRA) Practice Guidelines (2018):](#) A general rule is to start low and go slow but continue to increase the dose until the desired goals of treatment have been reached or side effects preclude dose increases or when maximum recommended dosage is reached.[4]

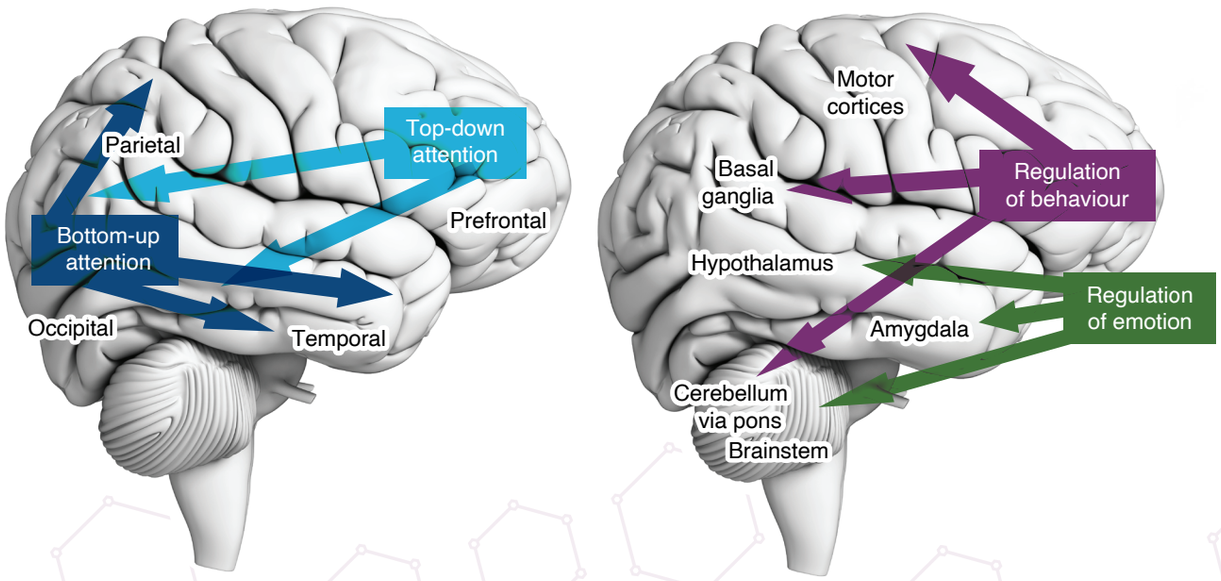
[National Institute for Health and Care Excellence (NICE) ADHD Diagnosis and Management (2018):](#) Titrate the dose against symptoms and adverse effects in line with the BNF or BNF for Children until dose optimization is achieved, that is, reduced symptoms, positive behavior change, improvements in education, employment and relationships, with tolerable adverse effects[10]

How does the Mechanism of Action (MOA) of Stimulants Relate to Titration?

Prefrontal Cortex (PFC) & Executive Function

- The abilities to regulate attention, behavior and emotion are collectively referred to as **executive functions**, which are **essential for organizing and planning for the future.**[11]
- The **PFC regulates executive functions** through networks of interconnected pyramidal cells. These networks excite each other to store goals/rules to guide actions and are highly dependent on their neurochemical environment, as small changes in the **catecholamines, norepinephrine (NE) or dopamine (DA), can have marked effects on PFC function**.[11]

FIGURE 2 - PFC Regulates Attention, Behavior and Emotion

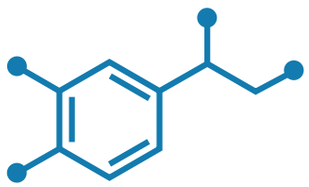


Adapted from Arnsten A. *CNS Drugs* 2009;23(Suppl. 1):33-41

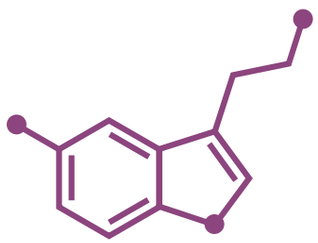
How does the Mechanism of Action (MOA) of Stimulants Relate to Titration? (cont.)

Synaptic Signaling in the PFC

- All currently **FDA approved ADHD medications** (stimulants and non-stimulants) are thought to act, at least in part, through their **impact on dopamine (DA) and/or norepinephrine (NE)**.[1,11]
  - Stimulants act directly to increase DA and NE levels and activity, whereas non-stimulants typically act directly on NE levels (or through adrenergic receptors) and may have indirect effects on DA levels.[1,11]
- Both **DA and NE are important modulators** of the **key PFC brain circuits** that support **attention, reward processing, and activity** levels and which are thought to **underpin ADHD**.[1,11]
  - **NE and DA are so critical to PFC function that depleting them is as detrimental as removing the cortex itself**.[11]
  - The **beneficial effects of NE** occur via stimulation of postsynaptic α_{2A}-receptors on the dendritic spines of PFC pyramidal cells, which initiates intracellular chemical events that lead to the closing of special ion channels. This series of events strengthens the connectivity of network inputs to the cell, thereby **increasing signals**.[11]
  - Conversely, the beneficial effects of **moderate amounts of DA** occur at D1 receptors, which act by weakening irrelevant inputs to the cells on another set of spines, thereby **decreasing noise**.[11]



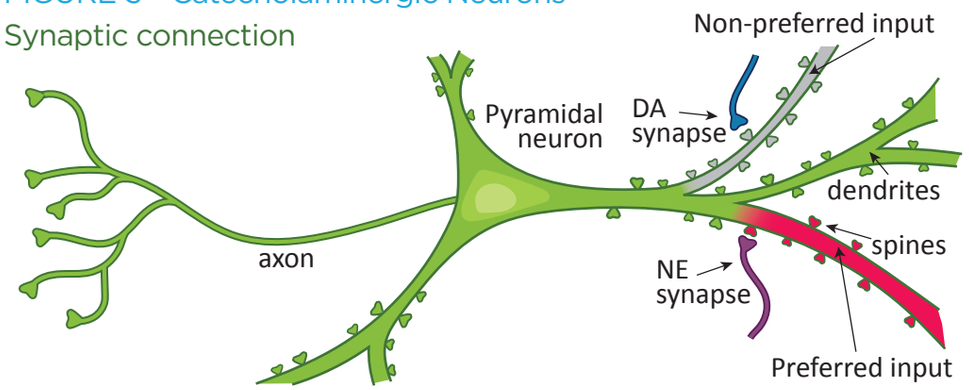
Norepinepherine



Dopamine

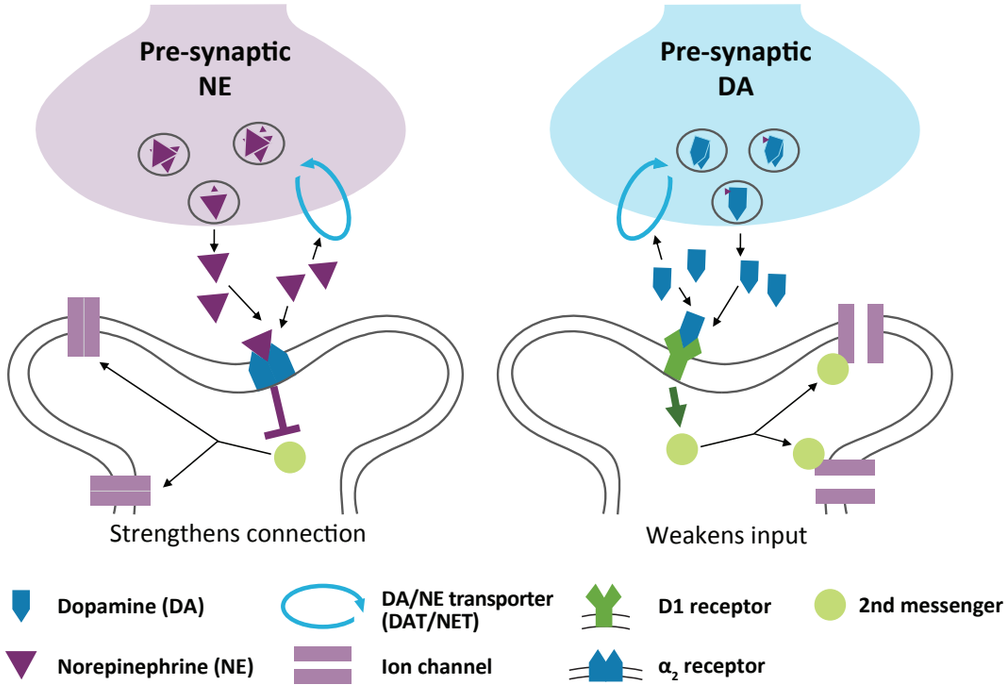
FIGURE 3 - Catecholaminergic Neurons

Synaptic connection



Adapted from Holt, CE, *et al. Nat Struct Mol Biol.* 2019;26:557–566

Post-synaptic pyramidal cell signaling in the PFC

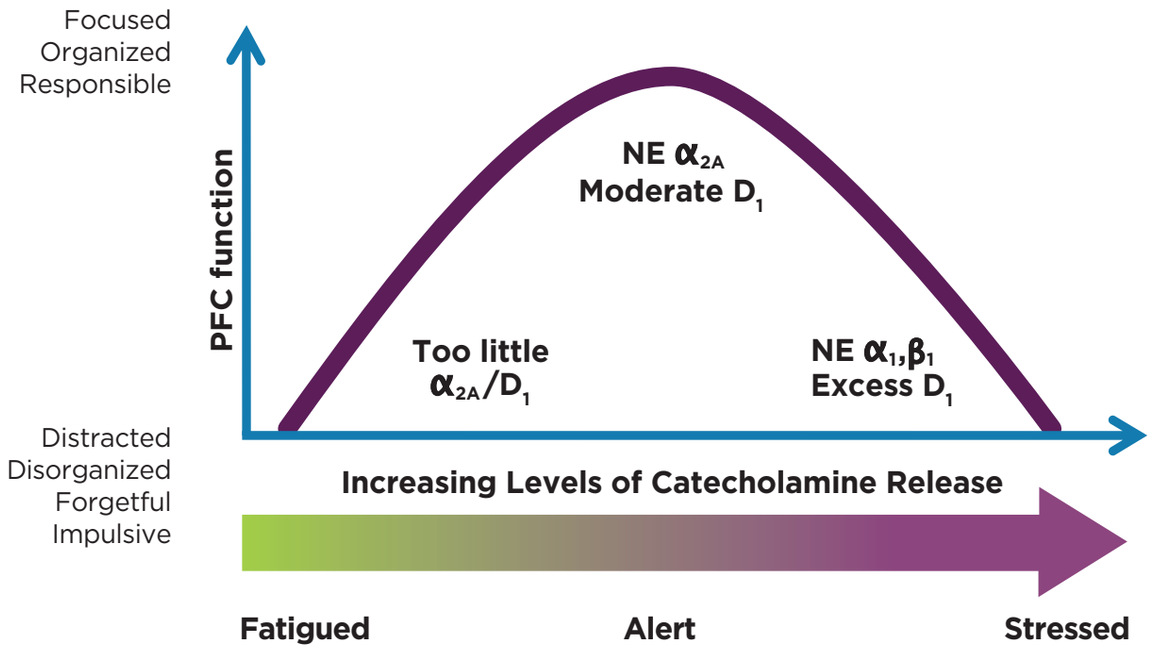


Adapted from Stahl SM. illustrated ADHD (Cambridge) 2009

How does the Mechanism of Action (MOA) of Stimulants Relate to Titration? (cont.)

PFC Requires an Optimal Balance of Catecholamines

FIGURE 4 - PFC is Sensitive to its Neurochemical Environment



Adapted from Arnsten A. *CNS Drugs* 2009;23(Suppl. 1):33-41

- As described by the inverted U-shaped curve, **both too little and too much DA and NE result in sub-optimal cognitive functioning** and are implicated in the development of side-effects and impairments.[1,11]
- **ADHD is associated with lower levels of DA and NE**, however:[1,11]
  - **Too much DA** is thought to be a key cause of **psychotic symptoms**[1,11]
  - **Excessive NE**, which activates lower-affinity α1 and β1 receptors, can lead to **anxiety, agitation or aggression**.[1,11]

- A key aim of **medication treatment is to optimize neurotransmission** through the important, predominantly glutamatergic, brain circuits, which function sub-optimally in ADHD.[1,11]
  - **Medications for ADHD correct the levels of DA and NE**, which modulate and correct the suboptimal glutamatergic transmissions.[1,11]
- **Over- or under -dosing or marked fluctuation in dose levels across the day** can compromise drug response, leading to **deterioration of symptoms and cognitive functioning**.[1]
- In children with comorbid autism spectrum and/or anxiety disorders, the therapeutic window of stimulants tends to be narrower and shifted to left, in the inverted U-curve.[1]
  - For this reason, these children are more often sensitive to medications and require lower doses to avoid side-effects such as over-focusing, agitation, anxiety and aggression.[1]
  - The general advice for commencing medication in ADHD individuals with comorbidities is to “start low and go slow”.[1]
- Experts recommend **asking about medication response within 3 or 4 hour-windows through the day**, in order to **titrate the dosage properly** across these windows throughout the day.[1]

What do Fixed- vs. Flexible-Dose Clinical Trials tell us about Titration?[2,12]

Background & Summary of Fixed- vs. Flexible-Dose Trials

Background

- **Fixed-dose trials are important during the drug-development process** of new medications to evaluate dose-dependency and inform efficacy and safety[2,12]
- However, if the data from **fixed-dose trials** are applied clinically, they **may lead to suboptimal dosing** or a dose with **intolerable side-effects**[12]
- **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**[2,12]

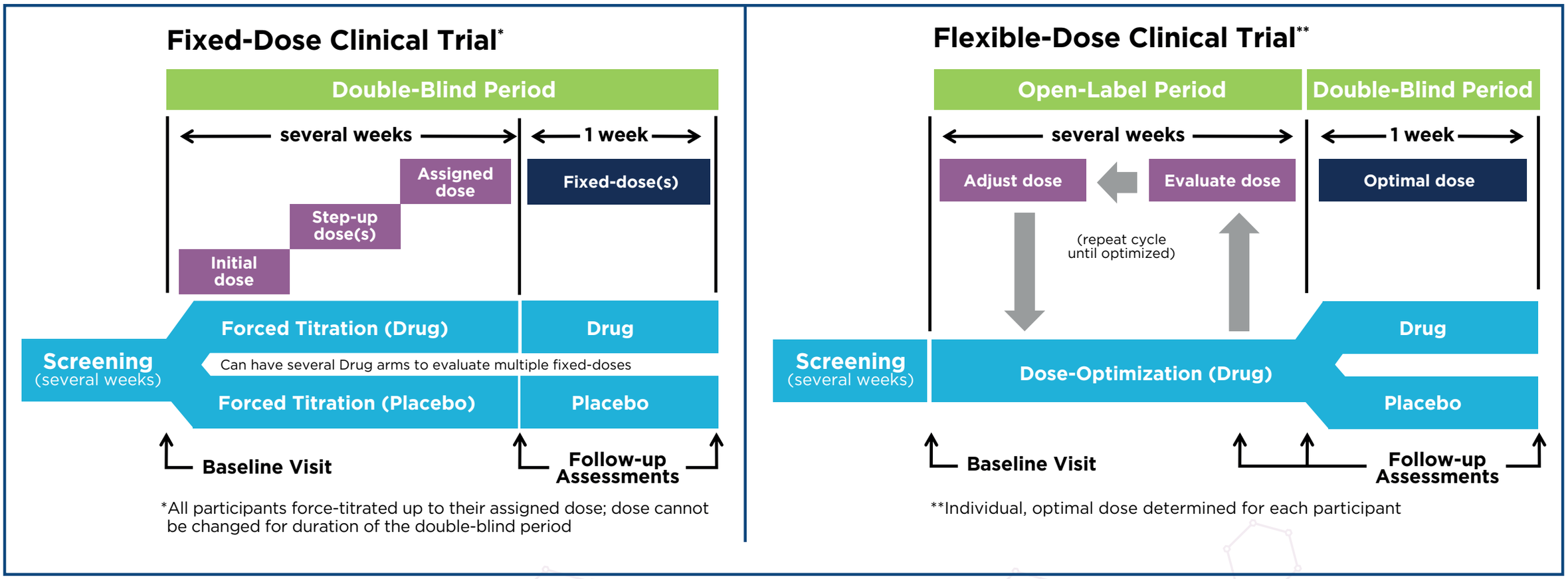
Based on a meta-analysis of 65 double-blind, randomized controlled trials of stimulants against placebo in 7,877 children and adolescents with ADHD, the following conclusions were drawn[2]:

Fixed-Dose Trials	Flexible-Dose Trials
There was a significant dose-response association between stimulant doses and efficacy and tolerability for both MPH and AMP	
There was an increased reduction in ADHD symptoms and *increased likelihood of discontinuation due to **AEs** with increasing stimulant doses*	There were increased reductions in ADHD symptoms *and reduced likelihood of discontinuations for any reason with increasing stimulant doses*
The added gains in efficacy decreased beyond 30 mg of MPH or 20 mg of AMP	The added gains in efficacy remained constant across the FDA-licensed dose range for MPH and AMP

What do Fixed- vs. Flexible-Dose Clinical Trials tell us about Titration?[2,12] (cont.)

Background & Summary of Fixed- vs. Flexible-Dose Trials

FIGURE 5 – Fixed-Dose vs. Flexible-Dose Clinical Trial Designs



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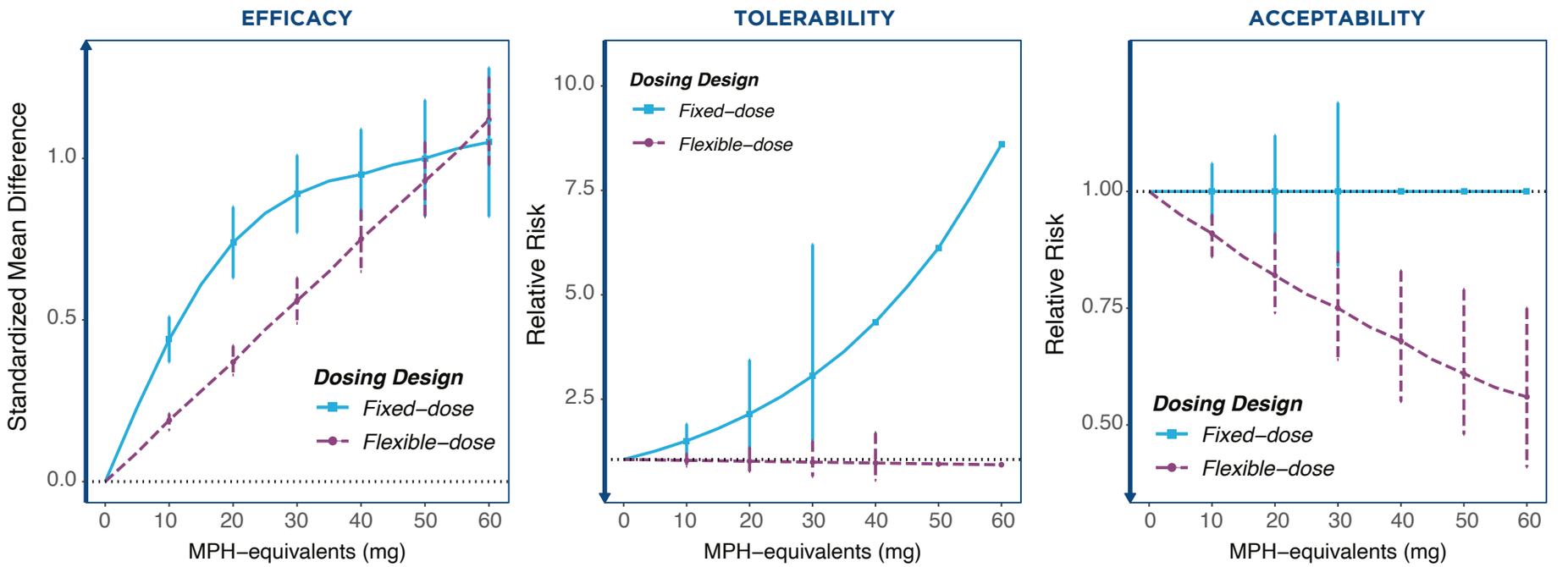
What do Fixed- vs. Flexible-Dose Clinical Trials tell us about Titration?[2,12] (cont.)

Results from the Meta-Analysis - as dose increases across the FDA-licensed dose range*:

FIGURE 6 – Dose-Response Curves for MPH

Methylphenidate (MPH)



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

Definitions

Efficacy
change in ADHD symptom severity scores on standardized scales

Tolerability
treatment discontinuation due to adverse events

Acceptability
treatment discontinuation for any reason

Adapted from Farhat et al. *Molecular Psychiatry*. 2022; doi.org/10.1038/s41380-021-01391-9

This meta-analysis 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.

What do Fixed- vs. Flexible-Dose Clinical Trials tell us about Titration?[2,12] (cont.)

Results from the Meta-Analysis - as dose increases across the FDA-licensed dose range*:

FIGURE 7 – Dose-Response Curves for AMP

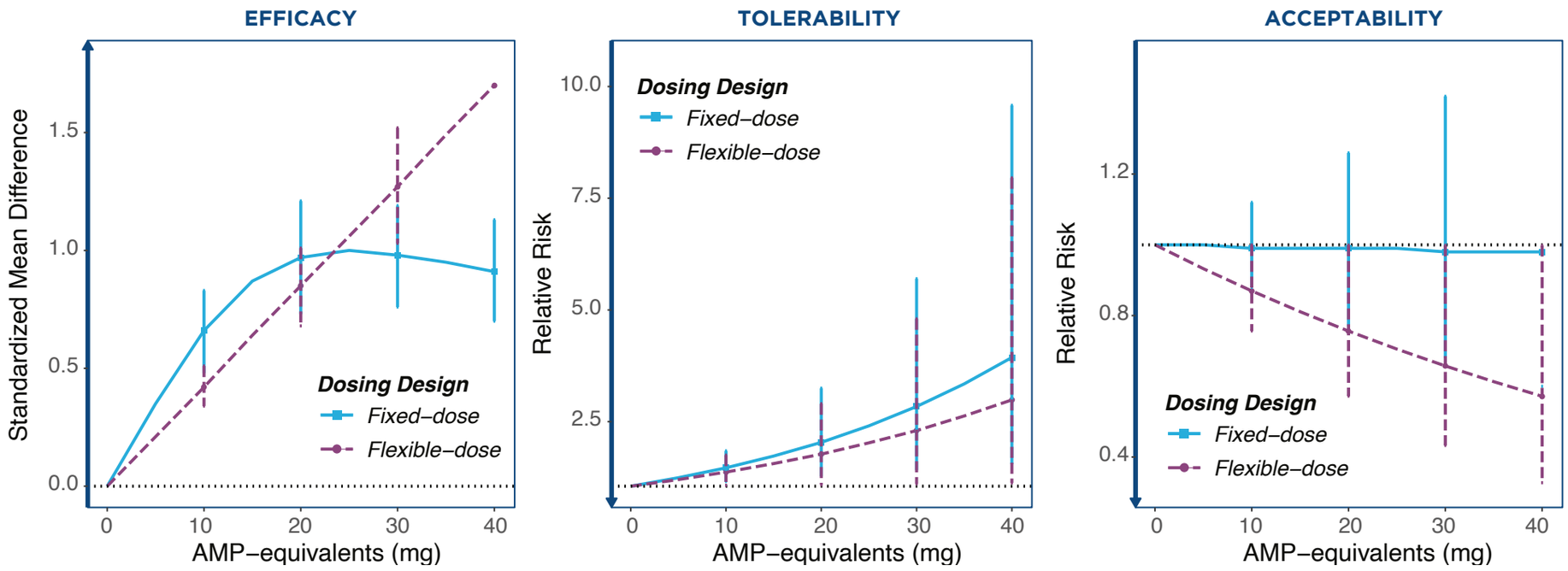
Amphetamine (AMP)

Definitions

Efficacy
change in ADHD symptom severity scores on standardized scales

Tolerability
treatment discontinuation due to adverse events

Acceptability
treatment discontinuation for any reason



Efficacy		Tolerability		Acceptability	
Fixed-dose	*Flexible-dose*	*Fixed-dose*	*Flexible-dose*	*Fixed-dose*	*Flexible-dose*
Diminishing returns beyond 20mg	**Improves** for every 10mg increase	**Worsens** for every 1mg increase	**Worsens** for every 1mg increase	**Stays the same** as dose increases	**Improves** for every 1mg increase

Adapted from Farhat et al. *Molecular Psychiatry*. 2022; doi.org/10.1038/s41380-021-01391-9

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Dose-Optimization Increases Efficacy and Improves Adherence[2]

Key Takeaways

- Suboptimal treatment of ADHD occurs when patients are not rigorously titrated, thus it is 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 the severity of ADHD symptoms and dose-limiting AEs.
  - Flexible titration mitigated the risks of discontinuing treatment 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
- Findings from fixed-dose and flexible-dose studies provided **compelling evidence in favor of titrating doses up to the maximum FDA-licensed doses** 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
- **Clear, evidence-based communication with families** about the importance of escalating doses could help decrease their concerns regarding flexible titration to higher doses

References and Abbreviations

References

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Abbreviations

AEs	Adverse events
α_1	Alpha 1 adrenergic receptor
α_{2a}	Alpha 2a adrenergic receptor
AACAP	American Academy of Child and Adolescent Psychiatry
AFP	American Academy of Family Physicians
AAP	American Academy Pediatrics
AMP	Amphetamine
ADHD	Attention Deficit/Hyperactivity Disorder
β1	Beta 1 adrenergic receptor
BNF	British National Formulary
CADDRA	Canadian ADHD Resource Alliance
DA	Dopamine
D_1	Dopamine receptor 1
FDA	Food & Drug Administration
MPH	Methylphenidate
NICE	National Institute for Health and Care Excellence
NE	Norepinephrine
PFC	Prefrontal Cortex

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