RESUMEN:

El trastorno por déficit de atención e hiperactividad (TDAH) es un trastorno del neurodesarrollo caracterizado por un déficit de noradrenalina y, por tanto, de las funciones ejecutivas como atención y control inhibitorio. El objetivo de este estudio fue revisar los datos de la literatura científica sobre la efectividad de diferentes tratamientos noradrenérgicos para el TDAH y sus efectos positivos y negativos (ventajas y desventajas). La declaración PRISMA se utilizó para realizar una búsqueda exitosa. Se establecieron las palabras clave con un rango de publicación del 2006 al 2021 en inglés como criterios de inclusión para la revisión. Tras realizar las fases de las guías, se decidió incluir un total 4 artículos de los 311 estudios iniciales ya que la gran mayoría eran en modelos animales y/o presentaban comorbilidades con otros trastornos. Todas estas búsquedas fueron realizadas en las siguientes bases de datos: Pubmed, Scopus y PubPsych. Los objetivos de estos artículos eran observar la eficacia de algunos de los tratamientos noradrenérgicos para el TDAH. En los resultados, se han observado una mejora significativa de los síntomas del TDAH en los 4 tratamientos noradrenérgicos utilizados (MPH $p<.05$, ATX $p<.01$, dasotralina $p<.008$ y COMB: D-MPH y GUAN $p<.02$). También se tuvieron en cuenta los efectos secundarios y las paradas de tratamiento debido a estos efectos, siendo el MPH y la dasotralina los que más paradas de tratamiento produjeron en las muestras. Por todo ello, se puede concluir que la atomoxetina parece la mejor opción. No obstante, hay muchos fármacos en desarrollo que están optimizando la eficacia y seguridad por lo que en futuras investigaciones se deberían tener en cuenta estos nuevos fármacos o, incluso, la confirmación de los efectos adicionales de la combinación de dos fármacos a largo plazo.

Palabras clave: tratamientos noradrenérgicos, TDAH, modelos humanos, revisión sistemática.

ABSTRACT:

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a deficit of norepinephrine and, therefore, of executive functions such as attention and inhibitory control. The objective of this study was to review the data from the scientific literature on the effectiveness of different noradrenergic treatments for ADHD and their positive and negative effects (advantages and disadvantages). The PRISMA statement was used to perform a successful search. Keywords with a publication range from 2006 to 2021 in English were established as inclusion criteria for the review. After completing the phases of the guidelines, it was decided to include a total of 4 articles from the 311 initial studies, since the vast majority were in animal models and / or presented comorbidities with other disorders. All these searches were carried out in the following databases: Pubmed, Scopus and PubPsych. The aims of these articles were to look at the efficacy of some of the noradrenergic treatments for ADHD. In the results, a significant improvement in ADHD symptoms was observed in the 4 noradrenergic treatments used (MPH p <.05, ATX p <.01, dasotraline p <.008 and COMB: D-MPH and GUAN p <. 02). Side effects and treatment stops due to these effects were also considered, with MPH and dasotraline producing the most treatment stops in the samples. Therefore, it can be concluded that atomoxetine seems the best option. However, there are many drugs in development that are optimizing efficacy and safety, so future research should consider these new drugs or even the confirmation of the additional effects of the combination of two drugs in the long term.

Kew words: noradrenergic treatments, ADHD, human models, systematic review.

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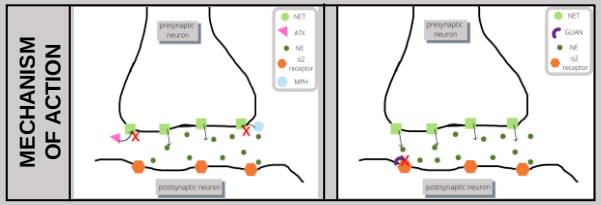
NORADRENERGIC TREATMENTS IN PATIENTS WITH ADHD: A SYSTEMATHIC REVIEW

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental and neurologic disorder characterized by impaired function of the prefrontal cortex (PFC), that mainly affects children. It is characterized by cognitive impairment and inappropriate levels of impulsivity, inattention and/or hyperactivity continuously at least 6 months previously of the diagnosis. The combination of symptoms can vary in children and adults depending of the subtype: inattention, hyperactivity/impulsivity and/or a combination of both.

The medications most widely used to treat ADHD include two types: stimulants and non-stimulants.



The **aim of this study** was to review the data in the scientific literature regarding the effectiveness of different noradrenergic treatments for ADHD and its positive and negative effects (advantages and disadvantages).

CONCLUSIONS

- Currently, ATX seems the better option for ADHD regarding efficacy and safety.
- Although Dasoltraline is effective, presents the highest rate of discontinuation due to adverse effects. Despite this, the side effects are mild to moderate and temporary.
- Future studies should assess long-term effects of the drugs to improve safety and efficacy. Also, it will be interesting to investigate deeply the efficacy of the combination of treatments such as guanfacine and d-MPH in preclinical and clinical trials.
- Limitations: To find articles in which patients do not present comorbidity with other disorders. In any study, the sample was not separate by gender because to study possible gender differences may be relevant.

METHOD

Key words: noradrenergic treatments, ADHD
published between 2006 and 2021

Pubmed n=158
Scopus n=148
PubPsych n=5

Records identified through databases searching (n=311)

Records after duplicates removed (n=306)

Records excluded for full-text not available (n=188)

Full-text articles assessed for eligibility (n=118)

Full-text articles excluded (n=114)

Studies included in the systematic review (n=4)

*** Exclusion criteria**: animal models, comorbidities of ADHD and drug abuse

4 articles reviewed

RESULTS

	AUTHORS	N	TREATMENTS	EVALUATION TESTS	RESULTS
STIMULANTS	Bron et al. (2013)	22 aged 18 to 55 years old ♀=5 ♂=17	Methylphenidate (MPH) - Placebo group - MPH group with a initial dose of 36mg/kg daily	CPT; ADHDRS; Side Effects Rating Scale; Adherence Questionnaire	● A significant improvement of deficit in executive function and a reduction of ADHD symptoms (p<. 05) ● Discontinuation of 13'6%
NON-STIMULANTS	Wilens et al. (2006)	601 aged 12 to 18 years old ♀=124 ♂=477	Atomoxetine (ATX) - Placebo group - ATX group with a mean endpoint of dose 1'41mg/kg/day	ADHDRS; CGI-S	● A significant improvement in symptoms and severity in the first 3 months (p<.01) ● Discontinuation of 5'2%
	Koblan et al. (2015)	331 aged 18 to 55 years old ♀=137 ♂=194	Dasotraline - Placebo group - Two groups of dasotraline: 4mg/day and 8mg/day	ADHDRS; CGI-S; WRAADDS; BPRS; CDR	● Major improvement for 8 mg group (p=0.008) ● Discontinuation between 10.3 and 27.8%
COMBINATION	McCracken et al. (2016)	212 aged 7 to 14 years old ♀=70 ♂=142	5-20 mg/day MPH 1-3 mg/ day Guanfacine (GUAN) Combitation (COMB) = MPH + GUAN with fixed flexible doce	CGI-S and ADHDRS; Physical Symptoms Checklist	● Major reductions in ADHDRS Inattentive subscale score for COMB group (p=.02) ● Discontinuation of 2'9%

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