1 Abstract

Title

Post-authorisation safety study to evaluate the long-term safety of dexamfetamine (Amfexa)

Marketing authorisation holder(s)

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Keywords

Dexamfetamine; Stimulants; ADHD; Children; Safety

Rationale and background

Dexamfetamine is a stimulant drug for the treatment of ADHD. There is a need for additional information about the safety of dexamfetamine in children concerning the incidence of cardiovascular diseases, psychiatric disorders, growth impairment and sexual maturity disorders.

Research question and objectives

1. To assess the incidence proportion and incidence rate for cardiovascular, psychiatric, growth and sexual maturity-related adverse events (AEs) in children with a diagnosis of ADHD who have been treated with dexamfetamine, methylphenidate or lisdexamfetamine in healthcare databases of three countries.
2. To compare the risk of long-term cardiovascular, psychiatric, growth and sexual maturity-related AEs of dexamfetamine versus methylphenidate or lisdexamfetamine in each database.

Study design

A retrospective study design was used where patients could enter and exit the study between 2015-2019.

Setting

Healthcare systems in the United Kingdom, Germany and United States (US).

Subjects and study size, including dropouts

Patients aged 6-17 years newly initiating dexamfetamine, lisdexamfetamine, methylphenidate or (for US only) dexmethylphenidate for the treatment of ADHD from 01 January 2015 were followed from first prescription of study stimulant to the date of an AE or the end of study time period (31 December 2019 inclusive for the current analysis).

Variables and data sources

Routinely collected healthcare data from The Health Improvement Network (IMRD, United Kingdom), Disease Analyzer (DA, Germany) (primary care) and PharMetrics Plus™ (US)

(administrative claims) were used. Data was used to classify and quantify drug exposure, identify AEs and adjust for potential confounding.

Results

Study stimulants were prescribed to 324,029 patients from 2015 through 2019 combined (IMRD: n=6,101; DA: 6,674; PharMetrics Plus™: 311,254). Dexamfetamine was least commonly prescribed (IMRD: 0.8%; DA: 1.4%; PharMetrics Plus™: 1.3%). For all AEs of interest, incidence rates and proportions were slightly or substantially higher in PharMetrics Plus™ than in IMRD and DA for all three stimulants.

Cardiovascular diseases were diagnosed in approximately 3% of users of the investigated stimulants in PharMetrics Plus™. The incidence rate ranged from 18.8 per 1000 patient-years for dexamfetamine to 21.8 for lisdexamfetamine. Psychiatric disorders were diagnosed in 9.3% of methylphenidate users, 10.3% of lisdexamfetamine users and 11.9% of dexamfetamine users. The incidence rate was 54.3 per 1000 patient-years for methylphenidate, 63.2 for lisdexamfetamine and 74.8 for dexamfetamine. Growth impairment was diagnosed in 4% of users of the investigated stimulants. The incidence rate ranged from 21.5 per 1000 patient-years for methylphenidate to 26.2 for lisdexamfetamine and 27.5 for dexamfetamine. Sexual maturation disorders were diagnosed in 0.5%-0.7% of users of the investigated stimulants. The incidence rate was 2.9 per 1000 patient-years for methylphenidate, 2.8 for lisdexamfetamine and 2.7 for dexamfetamine.

Unadjusted odds ratios (ORs) of single AEs often indicated higher risk associated with dexamfetamine than comparators. However, adjustment for confounding attenuated these direct associations toward non-significance of all associations with the exception of growth impairment; for cardiovascular disorders, the association became inverse upon adjustment, suggesting reduced odds of AEs associated with dexamfetamine but findings were not significant. In PharMetrics Plus™, the risk of growth impairment was similar to lisdexamfetamine, but significantly higher when compared to methylphenidate in both adjusted models (multivariably: OR = 1.202, 95% CI 1.054 to 1.371; propensity score matched: OR = 1.216, 95% CI 1.047 to 1.413) and in comparison to dexmethylphenidate in multivariate model (multivariably: OR = 1.155, 95% CI 1.010 to 1.320; propensity score matched: OR = 1.169, 95% CI 1.007 to 1.356). In the adjusted time-to-event analyses, dexamfetamine users seemed to have a higher risk of growth impairment compared to methylphenidate (multivariably: HR = 1.109, 95% CI 0.840 to 1.462; propensity score matched: HR = 1.075, 95 CI, 0.730 to 1.583) and dexmethylphenidate (multivariably: HR = 1.111, 95% CI 0.838 to 1.471; propensity score matched: HR = 0.997 (95% CI, 0.683 to 1.455)), but in contrast to the odds ratios, associations for both comparators were not significant.

When assessing any AE as a composite outcome, unadjusted ORs and HRs changed only marginally upon multivariable adjustment. In PharMetrics Plus™, dexamfetamine had increased odds ratios for composite outcomes in comparison to methylphenidate (multivariably adjusted: OR = 1.103, 95% CI 1.015 to 1.198; propensity matched: OR = 1.118, 95% CI 1.019 to 1.227), but not when compared to dexmethylphenidate (multivariably adjusted: OR = 1.078, 95% CI 0.989 to 1.175; propensity matched: OR = 1.065, 95% CI 0.970 to 1.168) or lisdexamfetamine (multivariably adjusted: OR = 0.993, 95% CI 0.913 to 1.080 and propensity matched: OR = 1.025, 95% CI 0.934 to 1.125). With the exception of the unadjusted one, all hazard ratios were not significant for any AE of interest in the composite outcome.

Discussion

The results suggest that there is no increased risk of cardiovascular, psychiatric or sexual maturity disorders associated with the use of dexamfetamine when comparing with other stimulants. In all databases, the odds ratio for sexual maturation disease was not increased in users of dexamfetamine compared to other stimulants, but only few events were

recorded. There might be an increased risks of growth impairment associated with dexamfetamine compared to methylphenidate, but the results were not conclusive. These results and in particular the possible association of dexamfetamine with growth disorders are currently mainly based on PharMetrics Plus™ and may not be fully generalizable for the European population.