ABSTRACT

A Brazilian Health Technology Assessment Bulletin (BRATS) article regarding scientific evidence of the efficacy and safety of methylphenidate for treating attention deficit hyperactivity disorder (ADHD) has caused much controversy about its methods. Considering the relevance of BRATS for public health in Brazil, we critically reviewed this article by remaking the BRATS search and discussing its methods and results. Two questions were answered: did BRATS include all references available in the literature? Do the conclusions reflect the reviewed articles? The results indicate that BRATS did not include all the references from the literature on this subject and also that the proposed conclusions are different from the results of the articles chosen by the BRATS authors themselves. The articles selected by the BRATS authors showed that using methylphenidate is safe and effective. However, the BRATS final conclusion does not reflect the aforementioned and should not be used to support decisions on the use of methylphenidate.

DESCRIPTORS: Child. Attention Deficit Disorder with Hyperactivity, Drug Therapy. Methylphenidate, therapeutic use. Evaluation of the Efficacy-Effectiveness of Interventions.
INTRODUCTION

The March 2014 issue of the Boletim Brasileiro de Avaliação de Tecnologias em Saúde (BRATS – Brazilian Health Technology Assessment Bulletin), published by the Brazilian Secretariat of Science, Technology, and Strategic Inputs, aimed at evaluating scientific evidence of the efficacy and safety of the treatment with methylphenidate in children and adolescents with attention deficit hyperactivity disorder (ADHD). The BRATS authors concluded that the studies were generally of low methodological quality, with few follow-up weeks and low generalization. They do not recommend using methylphenidate, despite the literature indicating otherwise.

Health technology assessments are extremely important, especially those applied in the Brazilian Unified Health System (SUS). Rational use of medicines should always be encouraged and any therapeutic strategy should only be used after a thorough clinical evaluation of the child, the family and his/her behavior at school and in the community. As a consequence of their dissemination and prestige, health technology assessments have the potential to be the main parameter for decision-making by public managers in Brazil. Therefore, documents such as this and their conclusions should not lead health professionals to doubts.16,b

The following two questions were established in order to critically review BRATS: 1) Did the report include all references available in the literature on the subject? 2) Did the conclusions proposed by the report clearly and objectively describe the results of the texts reviewed by the authors? In order to address these questions, we gathered researchers, professors and experts with extensive ADHD research knowledge.

SEARCH METHOD ANALYSIS

BRATS edition

The authors of the cited edition of BRATS performed searches in the following databases: Medline (PubMed), the Cochrane Library, the Centre for Reviews and Dissemination (CRD), the National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH). However, some databases that we consider relevant were not included, such as: the American Psychological Association (PsycINFO); Literatura Latino-Americana em Ciências da Saúde (LILACS – Latin American...
Literature in Health Sciences); Elsevier (Embase); and the Science Citation Index from the Institute for Scientific Information (ISI) from the United States, as well as their Web of Science and SciSEARCH search interfaces. The following key words were used for the aforementioned searches: “Methylphenidate”, “children” and “attention-deficit disorder”. However, this search strategy was quite restrictive because it made no use of electronic search mechanisms that are important for including all relevant articles from a large number of related terms, such as the “MeSH terms” mechanism in PubMed. In addition, the term “hyperkinetic disorders”, which was adopted by the International Classification of Diseases (ICD) and accepted and recommended by the Brazilian Ministry of Health for providing any mental health care in Brazil, was not included.

NEW SEARCH METHOD

We conducted another search, in accordance with the recommendations for systematic reviews. In this search, the terms “Methylphenidate”, “children”, “attention-deficit disorder” or “hyperkinetic disorders” were used. We found 563 studies in the Medline database with the same filters used by BRATS (Systematic Reviews; Randomized Controlled Trial; and Publication date from 1/1/2000 to 12/31/2013). We used the exclusion criteria proposed by BRATS and found 54 articles that were not included in the BRATS search.

The BRATS authors did not explain why, despite the significant number of studies with rigorous methodology on psychostimulants, they chose to include only seven studies, four of which were systematic reviews with meta-analysis, one was a randomized clinical trial and two were health technology assessments. It was clear that choosing these criteria dramatically reduced the number of assessed studies. From a methodological point of view, that fact alone makes any systematic review incomplete.

In regard to the results presented, only five of the seven articles were described in a table that presented different data (e.g., standardized mean difference, response rates, and medical difference) in a single column without clarifying the reasons for such decision. The studies considered were published from the year 2000 onwards, about children treated with methylphenidate compared with those given medicinal alternatives or placebos. Selection was directed by the inattention, hyperactivity, impulsiveness, adverse events, productivity and behavioral outcomes.

It is worth emphasizing that all articles had the following statements regarding methylphenidate use in children and adolescents: “presents significant superiority for reducing symptoms of hyperactivity compared with placebos”; “greater effectiveness than other medications”; “short- and long-term release have similar effects”. According to Schachter et al (2001), methylphenidate has an effect size of between 0.54 and 0.78, which is regarded as good, and proves the efficacy of methylphenidate for treating ADHD when compared with placebos. Prasad et al (2013) demonstrated the benefit of methylphenidate when compared to placebos, as well as the benefits of high doses when compared with low doses for the execution of tasks, productivity in the classroom and accuracy in school activities. Hanwella et al (2011) found that methylphenidate has efficacy and acceptability similar to atomoxetine, however the long-acting methylphenidate is more effective and should be considered as first-line therapy for children and adolescents with ADHD. Two other studies also concluded that treatment with methylphenidate was more effective than using buspirone or placebos.

COMMENTS

Despite the aforementioned, it is worth noting that the conclusions from BRATS are different from those presented in the original articles. More specifically, there are disagreements regarding the following points:

1. “(...) Evidence regarding the efficacy and safety of treatment with methylphenidate in children and teenagers, in general, is of low methodological quality, with a short follow-up period and little generalization capacity (...).”

This statement is contradictory because the authors themselves performed a study with many methodological biases, besides not specifying the criteria for including the five reviewed studies and for qualifying them as the only ones to present good methodological quality.

There are currently many articles of high methodological quality in the literature that were not included in BRATS, such as the Multimodal Treatment of Attention Deficit Hyperactivity Disorder Study (MTA). The MTA is one of the multicenter studies of high methodological quality on ADHD, funded by the National Institute of Mental Health and designed to evaluate the main treatments for ADHD, including behavior therapy, medication, and a combination of the two. Its results have been published in articles since 1999 and have shown that methylphenidate is effective and safe, in addition to significantly improving the child’s symptoms and quality of life, as well as that of the child’s family, peers and teachers. Methylphenidate is one of the most widely studied and used medications for treating ADHD. Its safety and effectiveness were duly confirmed by methodologically rigorous studies in children and adolescents.
2. “(...) heterogeneity among the studies was one of the most frequent problems in the selected systematic reviews (...)”.

The effectiveness outcomes, which were assessed by varied diagnostic criteria and instruments, presented heterogeneous results that, in general, did not show superior clinical benefit compared with pharmacological alternatives or with different doses and forms of methylphenidate (…).”

Based on the fact that the criteria used for selection were defined by the authors themselves, it is difficult to understand why articles with similar designs were not filtered. However, regardless of the assessment tools and outcome variables, the five studies chosen by the BRATS revealed moderate effect sizes when methylphenidate was compared to placebos.12,14 The fact that there are studies with different methodologies but similar results, in terms of effectiveness, reassures the effectiveness of methylphenidate.

The fact that different formulations have similar results is positive, as it indicates that using methylphenidate, in all its forms, is beneficial for patients.13

3. “(...) With regard to the drug’s safety profile, studies have shown that some of the most common adverse effects were: appetite suppression, increased alertness and euphoria, insomnia, headaches, stomach pain and dizziness (…)”.6

The literature describes such adverse effects at three grade levels: mild, moderate and severe. Despite the above sentence being correct, all five articles reported that the side effects of using methylphenidate were considered mild.2,3,7,9 The BRATS authors did not mention the frequency or intensity with which each adverse event occurs or anything about the importance of the side effects. Therefore, they did give the impression that these are common.

However, many studies in the literature showed that the possible side effects of methylphenidate are considered mild, are well tolerated and do not outweigh the treatment benefits.2,3 Methylphenidate, in its various forms, showed that not only it helps children with ADHD by reducing extreme and improper hyperactivity, but also it significantly improves attention and concentration as well as function execution in their various dimensions. Proper treatment makes it possible for the child to develop as fully as possible at school and in other environments, as well as in the cognitive, affective and social dimensions.

4. “(...) Currently, the drug is increasingly being consumed in Brazil, which is not yet sold on the domestic market as similar or generic. There is evidence in existence that states that children who do not have ADHD were being medicated and that cases of the disease were being needlessly treated (…).”

None of the studies included in the review were done in Brazil, so it was not clear how this evidence was shown. There has been an increasing rate of methylphenidate consumption in Brazil,6 due to the fact that the measurement starting point was zero. However, consumption of the drug is not greater than the disease’s prevalence, and national estimates indicate that ADHD is still undertreated.6 This point is of extreme relevance for future studies. In order to investigate the real reasons for the increase in the consumption of psychostimulants in Brazil, it is suggested that answers be given to relevant, among others, questions such as: 1) Is there any abuse of methylphenidate? If yes, in which population does it occur?; 2) Are there people with ADHD who do not have access to medication? 3) Has there been an increase in the number of recognized ADHD cases? 4) Is there any misuse of psychostimulants by professionals who have not been properly trained in child and adolescent psychopathology?

5. “(...) Diagnosing this disorder is dimensional, as it involves typical patterns of behavior of the age group and those presented by the individuals. Moreover, symptoms of the disorder can be found in the behavior of individuals with normal development (…).”

Despite this statement being correct, it gives rise to questions regarding the validity of the disorder that is not applicable to a document which supposedly uses the principles of evidence-based medicine. It would be essential to mention the several studies that show the family aggregation of the disorder, its environmental and genetic risk factors, the changes in cerebral structure and function found in diagnosed individuals and the functional losses that occur throughout the disorder’s development. All these studies reinforce the validity of ADHD diagnosis.

6. “(...) considering its high potential for abuse and dependence, it becomes urgent to have debates that address the current problem of improper methylphenidate consumption, alerting the population to its misuse, adverse effects and legal consequences (…).”

None of the cited articles discuss the potential for methylphenidate abuse and dependence. Therefore, it is not clear how the authors arrived at this conclusion. It is important to stress that several studies have shown that methylphenidate does not cause chemical dependence,6 which are results that invalidate the authors’ conclusions.

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6 Agência Nacional de Vigilância Sanitária (ANVISA). Prescrição e consumo de metilfenidato no Brasil: identificando riscos para o monitoramento e controle sanitário. Bol Farmacoepidemiol SNGPC [Internet]. 2012 [cited 2015 jan 31];2(2):1-14. Available from: http://www.anvisa.gov.br/sngpc/boletins/2012/boletim_sngpc_2_2012_corrigido_2.pdf
CONCLUSIONS

Based on the critical analysis of the BRATS, it was possible to respond to the questions included, namely: the BRATS did not include all references that are already available in the literature on the subject; the conclusions proposed by the authors were not based on the results of the five articles chosen by the authors. The conclusions arrived at by the BRATS need to be reviewed because they do not restrict themselves to researched facts and therefore do not obey the methodological rigor that is necessary in scientific studies, based on systematic reviews of the literature and evidence-based medicine studies. Therefore, such conclusions should not offer scientific support to strategies and public policies on the subject.

REFERENCES

1. Coghill D. The impact of medications on quality of life in attention-deficit hyperactivity disorder: a systematic review. CNS Drugs. 2010;24(10):843-66. DOI:10.2165/11537450-000000000-00000

2. Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, et al. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med. 2011;365(20):1896-904. DOI:10.1056/NEJMoa1110212

3. Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, et al. European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry. 2011;20(1):17-37. DOI:10.1007/s00787-010-0140-6

4. Hanwella R, Senanayake M, Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. BMC Psychiatry. 2011;11(1):176. DOI:10.1186/1471-244X-11-176

5. King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, et al. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Health Technol Assess. 2006;10(23):iii-iv, xii-146. DOI:10.3310/hta10230

6. Mannuzza S, Klein RG, Truong NL, Moulton JL 3rd, Roizen ER, Howell KH, et al. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. Am J Psychiatry. 2008;165(5):604-9. DOI:10.1176/appi.ajp.2008.07091465

7. Martinez-Raga J, Knecht C, Szerman N, Martinez ML. Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. CNS drugs. 2013;27(1):15-30. DOI:10.1007/s40263-012-0019-9

8. Mattos P, Rohde LA, Polanczyk GV. ADHD is undertreated in Brazil. Rev Bras Psiquiatr. 2012;34(4):513-6. DOI:10.1016/j.rbp.2012.04.002

9. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 1999;56(12):1073-86. DOI:10.1001/archpsyc.56.12.1073

10. Mohammadi M, Hafezi P, Galeha A, Hajjaghaei R, Akhondzadeh S. Buspirone versus methylphenidate in the treatment of children with attention deficit hyperactivity disorder: randomized double-blind study. Acta Med Iran. 2012;50(11):723-8.

11. Molina BSG, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry. 2009;48(5):484-500. DOI:10.1097/CHI.0b013e31819c23d0

12. Prasad V, Brogan E, Mulvaney C, Grange M, Stanton W, Sayal K. How effective are drug treatments for children with ADHD at improving on-task behaviour and academic achievement in the school classroom? A systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2013;22(4):203-16. DOI:10.1007/s00787-012-0346-x

13. Punja S, Zorzela L, Hartling L, Urichuk L, Vohra S. Long-acting versus short-acting methylphenidate for paediatric ADHD: a systematic review and meta-analysis of comparative efficacy. BMJ Open [Internet]. 2013;3(3):e002312. DOI:10.1136/bmjopen-2012-002312

14. Schachter HM, Pham B, King J, Langford S, Moher D. How efficacious and safe is short acting methylphenidate for the treatment of attention deficit-disorder in children and adolescents? A meta-analysis. CMAJ. 2001;165(11):1475-88.

15. Sonuga-Barke EJS, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry. 2013;170(3):275-89. DOI:10.1176/appi.ajp.2012.12070991

16. Vidal AT, Nascimento A, Aração E, Petramale CA, Almeida RT. O desenvolvimento do monitoramento do horizonte tecnológico no mundo e a proposta brasileira. Bisol Inst Saude [Internet]. 2012 [citado 2015 jan 31];14(2):171-8. Disponível em: http://periodicos.ses.sp.bvs.br/pdf/bis/v14n2/v14n2a07.pdf

17. World Health Organization. International classification of diseases and related health problems - ICD-10: tenth revision. Geneva; 1994.

The authors declare no conflict of interest.