Rational use of medicines, pharmaceuticalization and uses of methylphenidate

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> **Abstract** The rational use of medicines (URM) is considered one of the key elements recommended by the World Health Organization (WHO) for pharmaceutical policies. The excessive increase in the use of medicines in many countries has been identified as a major barrier to the achievement of URM and is part of a phenomenon called the 'pharmaceuticalization' of the society. This paper aims to present innitiatives to rationalize the use of methylphenidate and its limits in Brazil, considering the concept of pharmaceuticalization of the society. It is an exploratory study, based on a narrative review of the scientific literature. Controversies about the uses of methylphenidate make it a good example of this phenomenon and may help in the reflection and construction of new paths to the limits found by the concept of rational use of medicines.

> **Key words** Rational use of medicines, Pharmaceuticalization, Methylphenidate, Attention deficit disorder and hyperactivity

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Introduction

The rational use of medicines (RUM) is considered one of the key elements recommended by the World Health Organization (WHO) for medicine policies1. Brazil's National Medicines Policy (NMP), defines it as the the process which comprehends the appropriate prescription; timely availability at affordable prices; dispensation in adequate conditions; and consumption of efficient, safe and quality medicines in the recommended doses, during the time defined and the period indicated² and its promotion is part of the policy's priority guidelines.

The implementation of the RUM requires the development of strategies such as the selection of medicines, construction of therapeutic formularies, appropriate management of pharmaceutical services, appropriate use and dispensation of medication, pharmacovigilance, educating users about the risks of self-medication, and interrupting and changing prescribed medicines. Regulation strategies are also essential as they work as guides for relationships in production, commercialization and prescription, which, undoubtedly, are the aspects most prone to pernicious influences in the direction of the non-rational use of medicines.

There is also a series of habits and practices that prevent their effectuation, such as the multiplicity of pharmaceutical products registered as innovations and which are no different from the existing ones, the diffusion of consumption without evaluating the impacts of adopting a product, the negative judgement about practices that guide the rational use of medicines, which is often understood as an element that reduces the prescriber's autonomy, and the influence of the pharmaceutical industry. Moreover, interventions that promote the RUM produce a lack of trust for patients that have their beliefs reinforced by advertisement which encourage consumption instead of educating patients³.

The excessive growth in the use of medicines in many countries has been seen as an important barrier to the achievement of the RUM. According to Busfield4, such growth is well acknowledged and may be seen as a clear evidence of a phenomenon called 'pharmaceuticalization'. Pharmaceuticalization can be defined as the translation of the transformation of human conditions, resources and capacities into opportunities for pharmaceutical interventio5. These processes go beyond the medical or medicalized domains to comprehend other non-medical uses for lifestyle and cognitive or sexual performance enhancement among 'healthy' individuals.

Also according to Busfield⁴, if the main concern was formerly about the indiscriminate use of antimicrobials, nowadays psychopharmaceuticals, especially the methylphenidate, have become the object of attention to experts in the issue. Considered by the World Health Organization as the worlds' bestselling synthetic psychostimulatory, the medication with methylphenidate as its active ingredient only arrived in Brazil in 1998⁶.

According to the International Narcotics Control Board (2013), in 2012, the global production of methylphenidate reached a record high of more than 63 tons. Even though there has been an increase in the number of countries producing the substance over the past few years, the United States of America (USA) remain responsible for almost 97% of the total production. Still in 2012, the USA, Canada, Germany, Spain, Switzerland, the Netherlands, Brazil, Sweden, Israel, South Africa and Australia were some of the main consumers of the substance. The National Survey on Access, Use and Promotion of Rational Use of Medicines (PNAUM, for the acronym in Portuguese), a transversal study carried out in Brazil between 2013 and 2014, found out that the methylphenidate is one of the most used medicines for chronical diseases in children between 6 and 12 years old8.

The methylphenidate, which, in the 50s, had no definite use and was indicated for tiredness of the elderly, has now been the first therapeutic option for the Attention Deficit Disorder, with or without Hyperactivity (ADD/H) in children and adults. According to Ortega6, nowadays, the frequent use and the reliability associated with its effects serve as a reference to legitimate diagnosis. The use of the substance is controlled by an ordinance, SVS 344/98, and the medication can only be dispensed through a yellow colored Prescription Notice type "A", for medicines included in the A3 list, which comprehends psychotropic medications. The use of methylphenidate is object of a series of controversies, mainly because it is also used for the enhancement of cognitive performance in healthy individuals.

The Rational Use of Medicines and the Methylphenidate

Developed by the WHO at the end of the 1970s, when the world witnessed a boom of the pharmaceutical industry, the concept of RUM has been materialized into a public policy in the

present days, through a structuring strategy for its promotion: the implementation of the Essential Medicines (EM) List. These medicines are understood as substances that meet the priority needs of the population's health and must be used according to a certain rationality, and selected by criteria of efficiency, safety, convenience, quality and favorable cost comparison.

Recently, professional councils, the Ministry of Health and the National Health Council have started a movement that claims for efforts towards the construction of guidelines that support public policies for the rationalization of the use of the methylphenidate and the confrontation of situations of abuse9. In Brazil, the methylphenidate is not included in the National List of Essential Medicines (RENAME, for the acronym in Portuguese), established by the Ministry of Health. However, as States and Municipalities are relatively autonomous to include products according to their local specificities, it is already possible to notice some movements for the inclusion of this medication in some cities' lists. Under pre-established criteria, patients of Brazil's Unified Health System (SUS) can regularly receive methylphenidate in the ambit of the pharmaceutical policies of the state of Espírito Santo and in the cities of São Paulo and Campinas.

The state of Espírito Santo was the first one in the country to create an ordinance regulating the public dispensation of the medication, in September 2014¹⁰. Followed by the municipality of São Paulo, in June 2014¹¹ and finally by the city of Campinas, in October 2014¹². There are, however, some interesting differences between regulations in these three places. Criteria for the inclusion of the medicine in protocols, such as age and symptoms, concentration, field of specialization of the prescriber and place for dispensation are the main divergent items.

In Rio de Janeiro, the approval of a municipal act was not enough to structure a program for public dispensation¹³. In 2012, mayor Eduardo Paes approved draft act n. 710/2010, put forward by the city council member Tio Carlos, which guaranteed rights to students with ADHD in the municipality of Rio de Janeiro. The act addressed guidelines to be adopted by the city in order to educate parents and teachers about the Attention Deficit Disorder – ADHD, and also determined the availability of medicines associated with the treatment of the disorder in municipal public health facilities.

Amidst many controversies concerning the effectiveness of the medication in the treatment

of ADHD, in March 2014, the Brazilian Bulletin on Health Technology Assessment (BRATS) published a study that indicated that methylphenidate was a medication with "high potential for abuse and dependence" and that "there should be thorough assessment of the effect of methylphenidate on ADHD"14. According to the authors, the results found low methodological quality, short-term follow-up and low capacity for generalization in most of the studies about the efficiency and safety of the use of methylphenidate in children and teenagers. Still, the document concluded that there are evidences that children without ADHD receive the medication and in some cases the disorder is being unnecessarily treated. The diagnosis of the disease should be dimensional, for it involves typical patterns of age behavior and behaviors presented by individuals. Furthermore, symptoms of the disorder may be observed in individuals with regular behavior development. Machado et al. 15 present strong criticism to the publication and state that such conclusion cannot be found in the articles included in the study.

Uncertainties in diagnosis, frequent co-morbidities observed in ADHD and the relationship between the individual and school or work are factors that challenge the adherence to treatment protocols. Wannmacher¹⁶ states that therapeutic decision making, including the prescription of medicines, should be based on ethics. If on one hand, professionals must be permanently updated and aware that "science is mutable and permanently fostered by new evidences", it is also essential that such evidences are consolidated by scientific methodology that should produce grades of recommendation that are exempt from conflicts of interest and that consider the principles of autonomy, justice, non-maleficence and beneficence.

Therefore, based on the decision to build protocols for the use of methylphenidate as a way to rationalize use and through literature reports, the present article aims to debate the boundaries and challenges posed by the different types of medicine use.

Methodology

This is an explanatory study carried out based on a narrative review of scientific literature about the phenomenon of pharmaceuticalization, the rational use of medicines and uses of the methylphenidate.

The initial proposal for bibliographical research included the combination of the following

descriptors: "pharmaceuticalization", "rational use of medicines" and "methylphenidate". Considering the originality of the subject and the implicit conflict between practices of rational use of medicines and the effects of pharmaceuticalization, there were only three articles found, two under the combination "pharmaceuticalization" OR "pharmaceuticalisation" AND "rational use of medicines" in the Virtual Health Library (BVS)4 and Scielo¹⁷ and another one under "pharmaceuticalization" OR "pharmaceuticalisation" AND "methylphenidate" on PubMed-Medline and Scopus¹⁸. There was a new attempt made under the same bases, using the terms "pharmaceuticalization" OR "pharmaceuticalisation" AND "cognitive enhancement" which also resulted in one article19.

Such limitations required the inclusion of two other combinations: (Pharmaceuticalization OR Pharmaceuticalisation) AND "Label" (off-label)20,21, (Pharmaceuticalization OR Pharmaceuticalisation) AND "Mental Illness"22,23. It is important to note that, being a neologism, the word Pharmaceuticalization, in English, may be written with S or with Z, which was controlled in the research with the use of the Boolean operator "OR". The study also used the scientific database PubMed-Medline, Scopus and BVS and SciELO, with no time limit.

The inclusion criteria used articles published in fully available open access indexed journals. There were no exclusion criteria applied, considering the result of only 8 articles after the research carried out with the abovementioned combinations of keywords. The choice of not including the term "medicalization" clearly limited the findings on the subject, but enabled a better reflection on the production of arguments in the development of the several meanings of pharmaceuticalization. The bibliographic management was made with the Zotero software, version 4.0.21.2.

All articles were fully read and the analysis used a data extraction form composed of the variables: title, date of publication, objective, types of medicine use, ways to obtain the medication, elements contained in the concept of RUM.

The categories elaborated for the analysis of the works selected were initially the two main concepts of this article, that is, "pharmaceuticalization" and "rational use of medicines". Nevertheless, after an exhaustive reading of the articles, it was possible to notice that the off-label use plays a central role in the pharmaceuticalization process involving the methylphenidate. Therefore, the analysis also used the following categories as references: methylphenidate off-label use, rational use of medicines and pharmaceuticalization.

The categorization enabled the detailing and integration of the different subjects addressed in the articles and the outlining of a more comprehensive relationship between pharmaceuticalization and the different ways of using the methylphenidate.

Results and discussion

The initiatives for the construction of protocols for the public dispensation of methylphenidate are part of an initial movement in attempt to rationalize use and minimize inappropriate use of the medication²³⁻²⁶. Nonetheless, there are still uncertainties about who would benefit from the treatment and about the challenges to the establishment of diagnosis, which therefore challenge the construction of solid guidelines for the rational use of the medication. The articles found during the review are presented in Chart 1. Their contents detail important aspects that comprehend the phenomenon of pharmaceuticalization as an important barrier to practices of the rational use of medicines.

Regarding characteristics and behaviors which are similar to the ADHD, as occurs with other mental disorders, many individuals visit several experts searching for a solution to their difficulties, discomforts, pains and failures created by situations related to little or lack of attention²². Based on what is broadcasted by the media, patients look for professionals who will actually prescribe some sort of treatment. There are also those who intend to expand their cognitive capacity in order to take tests, to produce more in works that require more concentration, to increase productivity or even to reduce procrastination19 and also children and teenagers that meet the characteristics determined in diagnosis protocols.

There are several off-label uses, that is, uses that are different from those established in the leaflet. There are indications, posology, ways of administration and age ranges that are not the ones previously tested and approved²⁴. There is no official translation for the English term in Brazil²⁴. Busfield⁴ highlights the wide use of off-label prescription by doctors, the definition of some patients' behavior as "rational" and the non-conformity in some therapeutic schemes

Chart 1. Number and reference of articles found in a database.

Data Base/key-word	Scopus	Pubmed Medline	Bireme Lilacs	Scielo
(Pharmaceuticalization	Busfield J. Assessing the overuse of medicines. Soc	1*	0	Biehl J. Patient-
OR	Sci Med 2015; 131:199-206.	* the		Citizen-Consumers:
Pharmaceuticalisation)		same as		Judicialization
AND (Rational Use of		Scopus		of health and
Medicines)				metamorphosis
				of biopolitics. Lua
				Nova Rev. Cult.
				e Política 2016;
				98:77-105.
(Pharmaceuticalization	Vrecko S. Everyday drug diversions: A qualitative	1*	0	0
OR	study of the illicit exchange and non-medical	* the		
Pharmaceuticalisation)	use of prescription stimulants on a university	same as		
AND	campus. Soc Sci Med 2015; 131:297-304.	Scopus		
(Methylphenidate)				
(Pharmaceuticalization	Coveney C, Williams S, Gabe J. The Sociology	0	0	0
OR	of Cognitive Enhancemente: Medicalisation			
Pharmaceuticalisation)	and Beyond. Health Sociology Review 2011;			
AND (Cognitive	20(4):381-393.			
Enhancement)				
(Pharmaceuticalization	Towghi F. Normalizing Off-Label Experiments	0	0	0
OR	and the Pharmaceuticalization of Homebirths in			
Pharmaceuticalisation)	Pakistan. Ethnos 2014; 79(1):108-137.			
AND Label (off label)	Bell SE, Figert AE. Medicalization and			
	pharmaceuticalization at the intersections:			
	Looking backward, sideways and forward. Soc Sci			
	Med 2012; 75(5):775-783.			
(Pharmaceuticalization	Kokanovic R, Bendelow G, Philip B. Depression:	2*	0	0
OR	the ambivalence of diagnosis. Sociol Health Illn	* the		
Pharmaceuticalisation)	2013; 35(3):377-390.	same as		
AND Mental Illness	Fisher JA, Cottingham MD, Kalbaugh CA.	Scopus		
	Peering into the pharmaceutical "pipeline":			
	Investigational drugs, clinical trials, and industry			
	priorities. Soc Sci Med 2015; 131:322-330.			

considered "irrational" or "non-rational" as important aspects of the discussion about the excessive use of medicines.

Among the many roles of Anvisa, Brazil's National Health Surveillance Agency, the regulation of the medical practice is not one of them. Therefore, there is no way to establish any sort of control for prescriptions that result from this professional practice, which makes it possible that the medication be approved for one objective and prescribed for another one, which can be completely different from the uses tested in clinical trials^{23,24}. In the case of methylphenidate, the leaflet registered at Anvisa gives the prescriber the responsibility to determine doses and treatment

schedules. Consumption data indicate a more frequent use during school days, especially on the second semester of the year, which may be influenced by the off-label uses of the substance. The fact that it has mostly mild collateral effects may encourage the use of more powerful substances or the increase of the dose-response relationship.

Osorio-de-Castro et al.²⁵ affirm, however, that the use of medicines is not only motivated by health needs. Unlike the rational use (RUM), there are parallel non-rational "practices and desires" developed for the use of pharmaceutical substances by individuals and populations"^{25,26}. The outreach and popularity of a medication is not only based on its capacity to achieve an ef-

fect, but on its interaction with cultural and social pressures that define a condition as worthy of pharmaceutical resolution^{20,23}.

Busfield⁴ suggests a typology that considers five types of inappropriate use: a) not receiving medicines that are clinically necessary (benefits would compensate for the risks); b) receiving/ using medicines that are not efficient for the condition being treated (risks exceed benefits); c) receiving/using medicines with no appropriate clinical need (risks exceed any benefits); d) receiving/using a specific medicine, but in wrong doses or schedules or in combination with another incorrectly prescribed medicine (which would change the risk-benefit equation); e) receiving/ using expensive medicines, while there would be an equally efficient and cheaper alternative.

According to Osório-de-Castro et al.25 there are some factors that encourage this practice: the great availability (in quantity or variety) of medicines considered essential or not; the attraction caused by therapeutic novelties¹⁷; the powerful marketing strategies of the pharmaceutical industry; the supposedly inalienable right of the doctor to prescribe; and even cultural syncretism, which exposes medicines to uses never imagined by the professionals who originally developed them²⁰.

In the case of methylphenidate, as a controlled medicine that can only be sold with the retention of the prescription, there are two important resolutions that regulate its advertisement and commercialization. The first one is a Resolution of the Board Directorate (RDC) n. 96/2008 which addresses advertisement, publicity, information and other practices for the commercial advertisement of medicines, and resolves that its advertisement or publicity can only occur in journals with exclusively technical content, concerning pathologies and medicines directly, and exclusively directed at health professionals which are authorized to prescribe and/or dispense medicines²⁷. The second one is RDC n. 63/2008, which prohibits the online commercialization of medicines regulated by Ordinance n. 344/98, and only allows their purchase in person, in pharmacies²⁸. However, such regulation has not been enough and internet has made it possible to go beyond the access to information, creating environments in which medicines are easily located and obtained with no intervention from doctors or any other health authorities.

The access to an infinity of information sources available online has an essential role in the formation of this active posture of the individual that decides to use psychopharmaceutical substances such as methylphenidate. The new virtual environments for information sharing change or interfere in the relationship with doctors who are no longer supreme holders of knowledge and are now being questioned by patients who are every time more informed²⁹.

Between the years 2009 and 2011, Vrecko¹⁸ coordinated a qualitative research whose subjects were users of Aderall (a mix of amphetamine salts, also used for ADHD and forbidden in Brazil) which used the medication for cognitive enhancement in English universities. The results of the study revealed the following ways of obtaining the medicine for non-therapeutic use: friends, family members, parallel market and doctors who are "misled" by patients.

Their supply usually consists of a few pills and is not regularly maintained. People who receive it do not ask for it directly due to the risk of including the supplier in an embarrassing situation, but there were strategies reported to seduce and manipulate suppliers in order to obtain the medication. Obtention among friends and through family members or intimate partners does not involve financial gains but is more imposing than the previous one. The interaction with a close relative makes the "object" (the medicine) seem as common as any other one. It also includes strategies that are not observed among friends. In the parallel market, by its turn, interactions are impersonal and involve money. According to Vrecko¹⁸, data collected in interviews show that suppliers were not dealers, but acquaintances, "a friend's friend", and the transaction required the mobilization of a social network. It was clear that it is essential to trust friends who are willing to intermediate relationships for supply. It was also possible to notice that, when the medication was acquired this way, in exchange for money, it started to gain the connotation of 'drug', associated with the use in the streets, danger, illegality and was less perceived as a 'medication' that, in comparison, was presented as relatively safe and socially accepted. The last way of obtaining the medication presented in the study was by misleading doctors, which involved fraudulent and previously planned ways to fake symptoms that would lead to a (fake) diagnosis of ADHD and consequently a prescription for the desired medication. With the obtention of a prescription, the pattern of use changes and individuals start to take the medicine regularly instead of intermittently, as occurred when they accessed them through friends or in the parallel market.

One of the fundamental aspects of the society's pharmaceuticalization is the role played by means of communication in the diffusion of this phenomenon. Bedor³⁰ critically analyses the public introduction of a therapeutic non-hormonal option to "cure" disorders associated with women's bodies in menopause and post-menopause. The publicity campaign, according to the author, explored the pharmaceuticalization of ageing and mainly the constant search for the normalization and standardization of the female body. With an increase in the offer of new technologies that enable older individuals to have better quality of life, the medication abovementioned represented the outreach of the pharmaceutical industry in a situation that was naturalized as part of ageing. The innovation presented by the marketing strategy aims to neutralize the idea that desire and sexuality are exclusive to younger individuals. Another example is the Woloshin & Schwartz³¹ research on the current media coverage of the "restless legs syndrome". According to the authors, the means of communication have promoted a great exhibition for public opinion by exaggerating information about symptoms and the need for treatment, which resulted in cases of overdiagnosis. Journalistic essays (paid or not) and online interactions play a leading role in the non-rational use of methylphenidate.

Self-medication is also an increasing way of consumption among those who use this mean of communication. Knowledge and the exchange of experiences are seen as "sources of wisdom" and turn interested individuals into "experts"32. The high level of specialization in patients with terminal diseases (in some cases acting in partnership with the doctor) was already perceived by researchers, but in the pharmaceuticalization expansion process it happens mainly with substances used for non-therapeutic use, aimed at performance enhancement, named by Conrad³³ as "biomedical enhancement". In that case, "enhancement" would represent a social good within a culture that values "more, bigger, and faster!" and in which competitive differences between individuals are seen as a pathology. Methylphenidate has been the protagonist in this process for cognitive improvement/enhancement.

According to Bostrom & Sandberg³⁴, "cognition can be defined as the processes an organism uses to organize information. This includes acquiring information (perception), selecting (attention), representing (understanding) and retaining (memory) information, and using it to guide behavior (reasoning and coordination

of motor outputs)". Interventions to improve cognitive function may be directed at any one of these functions. When an intervention aims to correct a specific pathology or defect of a cognitive subsystem, it may be characterized as therapeutic. The lack of studies does not yet enable the determination of abuse in the different ways of using the methylphenidate, but the use among healthy individuals is evident.

Bostrom & Sandberg³⁴ claim that life in the modern society demands a whole lot more study and intellectual concentration than was expected for the human species in its environment of evolutionary adaptation and therefore it is not surprising that many people struggle to meet school or job market demands with the use of new technologies. The use of these tools for cognitive enhancement can be seen, according to the author, as an extension of the human species capacity to adapt to the environment.

Even though data on off-label medicine use for cognitive enhancement are difficult to obtain, recent researches indicate that it is widely diffused among students. Based on studies on the illegal use of stimulators, 5-35% of North American university students use or have already used stimulators prescribed for ADHD³⁵. In Brazil, there has been a significant increase in the diffusion of the disorder and in the number of people who started to access substances for the treatment of ADHD and, in addition, there are data indicating an increase in the consumption of methylphenidate for non-therapeutic use³⁶. Health authorities claim that there is indication of abuse and deviant use for non-therapeutic reasons. Even though there are efforts currently being made, it is still hard to quantify the effects of the prescription of medicines for cognitive enhancement in healthy individuals²⁹.

Amidst debates about the ethical dilemmas of medicine use for cognitive enhancement in healthy individuals, there are questions involving addiction, ways of use and access. It is not possible to precisely determine whether people who need free commercialization stimulators such as coffee, energetic drinks and nicotine in order to keep a regular cognitive level would actually become addicted in case they started to use these medications. Cakic³⁷ defends the need to create strategies to minimize risks and boost benefits, for students will use medicines to increase their cognitive capacity (nootropics) disregard their safety or legality. And finally, since they will never be accessible to all, new ways of inequalities may arise.

The paths walked towards the development and regulation of new medicines call attention to ways in which pharmaceuticalization, biomedicalization and medicalization processes often converge and superpose each other, contributing to the sociological debate of enhancement^{19,20}. However, Coveney et al.¹⁹ highlight that when the object of analysis is a medication, the concept of pharmaceuticalization should enable the understanding of its different insertions in the society, which may occur in the absence of medicalization or involvement of the medical professional. They highlight that, in the field of cognitive enhancement, this concept can only be applied to pharmaceutical ways and that ways which include the interface with computers or food should involve concepts such as medicalization and biomedicalization.

Coveney et al.19 suggest agendas of sociological studies in the field of pharmaceuticalization that include the detailing of the type and function of pharmaceutical products under development; economic, political, social and cultural trends existent in the conduction of these developments; ways of interacting with and understanding users, with pharmaceutical technologies that may be related to medicine or not; legitimation in different social and cultural contexts; and the evaluation of the pharmaceutical intervention in cognition and its consequences in bodies, beings and finally in the contemporary society. Therefore, new contributions shall arise and break the boundaries found by the current concept of rationality in the use of medicines.

Conclusions

The concept of pharmaceuticalization has made it possible to explore fields still not well analyzed in the use of medicines, with special focus on discussions about self-medication and the use of pharmaceutical technologies for cognitive improvement or enhancement. Studies in the field of health anthropology and sociology have presented new characteristics about the use of pharmaceutic substances, new ways of communication and also the role of the prescriber in this

Abuse and unnecessary use have increased, highlighting inadequacies in regulation, commercialization, publicity measures, prescription habits and cultural education of the population, among others. Therefore, thinking of an alternative to promote rationality for "enhancement" is a complex task, which involves several social actors and different systems, including social, economic, educational, epistemological and clinical aspects. Analyzing the proposal for public dispensation of methylphenidate as a way of rationalizing its use is also a challenge posed, since it is not yet clear which elements would be necessary for the diagnosis of individuals who have benefited from the medicine.

The governmental capacity to produce answers through regulations or by the construction of protocols is gladly received as an important measure, but it does not seem to be sufficient to detain the progress of advertisement and commercialization, which transform methylphenidate into one of the world's currently most used medicines.

Collaborations

A Esher and T Coutinho participated in all stages including the conception, design, writing and final revision of the article.

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