The self-reported prevalence of methylphenidate use by Master of Medicine (MMed) students registered at a South African university

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Declaration

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

Date: December 2022

Abbreviations

ADHD	Attention-deficit-hyperactive-disorder
MMed	Master of Medicine degree
FMHS	Faculty of Medical and Health Sciences
COMT gene	Catechol-O-methyltransferase gene
PAWC	Provincial Administration of the Western Cape
NHLS	National Health Laboratory Services
REDCap	Research Data Electronic Capturing Consortium

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CHAPTER 1

Abstract

Background. Methylphenidate is mainly used for the treatment of attention-deficit-hyperactive-disorder (ADHD). Its effect of increased attentiveness leads to the potential of off-label use by students for academic enhancement - previously demonstrated in undergraduate students. No publication exists on postgraduate student use of methylphenidate.

Objectives. To provide a summary of the self-reported prevalence and correlates of methylphenidate use in Masters of Medicine (MMed) students registered at the Faculty of Medical and Health Sciences of a South African university.

Methods. A cross-sectional study was conducted. Data was collected via a self-administered anonymous online questionnaire distributed by email to 505 registered MMed students.

Results. Of the 253 responses (response rate 50.1%) received 71 (28.1%) have used methylphenidate. Only 2.4% have been diagnosed with ADHD. The majority (73.2%) obtained it without a formal medical consultation. Self-prescription (26.8%) and prescription by a colleague without consultation (23.9%) contributed significantly. Academic performance enhancement was the primary motivation for use in 71.8% and 42.3% of users started using methylphenidate while registered as an MMed student. There was no statistically significant difference in terms of gender (p=0.151), age (p=0.288) or year of study (p=0.149).

Conclusions. Off-label use of methylphenidate is prevalent in MMed students registered at this South African university. The prevalence is significantly higher than in undergraduate medical students. The non-conventional means of access is of great concern. Efforts should be made to discourage self-prescription, educate students on the dangers of methylphenidate use, promote better access regulation and enhance psychological support.

Abstrak

Agtergrond. Metielfenidaat word hoofsaaklik voorgeskryf vir die behandeling van aandag-gebrek-hiperaktiwiteit-sindroom (AGHS). Die effek van verhoogde aandagspan lei tot potensiële misbruik deur studente vir akademiese doeleindes. Dit is voorheen in voorgraadse studente beskryf. Geen publikasie bestaan rakende die gebruik van metielfenidaat deur nagraadse studente nie.

Doelstellings. Om 'n opsomming van die selfgerapporteerde voorkoms van metielfenidaat gebruik in Magister van Medisyne (MMed) studente geregistreer aan die Fakulteit van Gesondheidswetenskappe van 'n Suid-Afrikaanse universiteit te beskryf.

Metodes. 'n Beskrywende deursnitstudie is uitgevoer. Data is by wyse van 'n anonieme webgebaseerde vraelys bekom. Dit is per e-pos aan 505 geregistreerde MMed studente versprei.

Resultate. Van die 253 reaksies ontvang (reaksie syfer 50.1%) het 71 (28.1%) metielfenidaat gebruik. Slegs 2.4% is met AGHS gediagnoseer. Die meerderheid (73.2%) het dit sonder 'n mediese konsultasie bekom. Voorskrifte aan self (26.8%) en voorskrif deur 'n kollega sonder konsultasie (23.9%) het grotendeels bygedra. Akademiese bevordering was die primêre doelwit vir gebruik in 71.8% van gebruikers en 42.3% het gedurende MMed studies dit die eerste maal gebruik. Daar was geen statistiese verskil in terme van gebruik in geslag (p=0.151), ouderdom (p=0.288) of jaar van studie (p=0.149) nie.

Afleidings. Nie-mediese gebruik van metielfenidaat gebruik is prevalent in MMed studente aan hierdie Suid-Afrikaanse universiteit. Die voorkoms is aansienlik hoër as in voorgraadse mediese studente. Die onkonvensionele metodes van toegang is kommerwekkend. Pogings moet aangewend word om voorskrifte aan self te beperk. Studente moet opgevoed word oor die gevaar van metielfenidaat misbruik, beter toegangbeheer moet toegepas word en sielkundige ondersteuning moet gebied word.

CHAPTER 2

Introduction/background

Methylphenidate is mainly used for the treatment of attention-deficit-hyperactive-disorder (ADHD).[1] The effect of its increased attentiveness leads to the abuse potential by students for academic enhancement.

It has been shown throughout the international[2],[3],[4],[5] and South African[6],[7],[8],[9] literature that the self-reported prevalence of methylphenidate use by undergraduate university students is significantly higher than the prevalence of ADHD.

However, research is inconclusive whether it subjectively improves academic performance.[10],[11],[12] Furthermore, methylphenidate can have serious life-threatening side-effects.[13]

The prevalence of methylphenidate use by postgraduate students was not researched to date.

Rationale

The use of Methylphenidate is not without risks and may have various life-threatening side-effects. The investigators found it necessary to establish the prevalence of methylphenidate use by Master of Medicine (MMed) students. In order to determine the prevalence of methylphenidate use by MMed students at the Faculty of Medical and Health Sciences of the University of Stellenbosch the investigators performed a cross sectional descriptive study.

Aim

To describe the self-reported prevalence of methylphenidate use and correlates by MMed students registered at the Faculty of Medical and Health Sciences of a single South African university.

Primary Objective

To provide a descriptive summary of the self-reported prevalence and correlates of methylphenidate use in MMed students registered at the Faculty of Medical and Health Sciences (FMHS) of a single South African university.

Secondary Objectives

- To provide a limited demographical description of the group with prevalent methylphenidate use. This included gender, year of study, and age group of the participants.
- To describe the prevalence of formally diagnosed ADHD and perceived ADHD without a formal diagnosis in the participants.
- To describe the pattern of use and acquisition of methylphenidate in the group of participants that has used it before. This included frequency of use, when it was used for the first time, motivation for use and side-effects experienced.
- To describe the prevalence of participants that are aware of a colleague using methylphenidate for academic purposes.

Hypothesis

No hypothesis as this was a descriptive study.

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CHAPTER 3

Literature review

Methylphenidate is classified as a central nervous system stimulant and is chemically similar to the amphetamines.[1] It is mainly used for attention-deficit/hyperactivity disorder (ADHD) and is also approved for the treatment of narcolepsy.[2] It is occasionally used for major depression refractory to conventional treatment.[1]

Methylphenidate is an indirect agonist and acts by inhibition of uptake of the neurotransmitters noradrenalin and dopamine.[2] Furthermore methylphenidate facilitates the secretion of dopamine and noradrenalin in the synaptic cleft as well as the inhibition of breakdown by monoamine oxidase.[3] There is some evidence that the manipulation of the dopamine transport system by methylphenidate may lead to indirect augmentation of serotonin action.[1] The exact mechanism on serotonin action is still unclear at this stage.

The clinical effect is decreased hyperactivity and distractibility, increased attentiveness and reduced impulsivity.[1],[4] Mild euphoria, a decreased sense of fatigue and increased completion of tasks are furthermore achieved.[1] These clinical effects has been shown to improve cognition if there is pathology rendering it suboptimal.[5]

The effect of increased attentiveness and ability to concentrate leads to the abuse potential of methylphenidate amongst students. The majority (68.3%) of methylphenidate users in a sample of undergraduate students at a South African University started using it during undergraduate studies.[6] Students use it mainly for academic purposes, especially during periods of high academic stress like exams.[7] “Academic purposes” includes an attempt to increase concentration, attention, alertness, academic performance and to combat fatigue to study.

A minority of the methylphenidate users use it for weight loss (1%) and social or recreational purposes (5%) in a sample of South African undergraduate medical students at a single

university.[8] Suppression of appetite is a well-known side effect[1] and may lead to abuse for the purpose of weight loss.

Current literature is inconclusive on whether psychostimulants such as methylphenidate improve cognition in healthy individuals. Mommaerts et al[9] suggested that methylphenidate does not enhance cognitive performance in people not formally diagnosed with ADHD. In 2016 research[5] done in Sau Paulo found that there is no objective difference in cognition between healthy subjects using methylphenidate in various different dosages (10-40mg) compared to placebo. The suggestion was that the subjective impression that methylphenidate improves cognition could rather be attributed to the feeling of wellbeing induced.

In contrary Linssen et al[10] did a meta-analysis of available literature in 2014 and found that methylphenidate improves working memory and processing speed in healthy individuals. Verbal learning and memory was also slightly improved, but visual learning and memory was unchanged.

Some highly functioning subjects and subjects homozygous for the met allele of the COMT gene even had impaired cognitive function using stimulants related to amphetamines compared to placebo.[11]

The prevalence of ADHD in the general adult population is 2.5%.[12] Yet methylphenidate use by university students for non-medical purposes is widely reported in international[13],[14],[15],[16] and South African[17],[6],[8],[18] literature with self-reported lifetime prevalence of psychostimulant use ranging from 5%[19] to 35%[20]. Faraone et al did a systematic review on 109 studies in 2019 and found that the self-reported non-medical stimulant use varies widely based on the different definitions used, methodology and study population surveyed.[13]

Two studies specifically evaluated the methylphenidate[17] and psychostimulant (including methylphenidate, dextroamphetamine, pemoline and modafinil)[8] self-reported use by undergraduate medical students at South African universities. Methylphenidate was used by

11% of participants at the time of the one study[17] whereas 18% of students reported a lifetime use of psychostimulants in the other[8].

Lifetime use in itself is not a true indicator of the magnitude of nonmedical use by university students and therefor the frequency of usage needs to be taken into account as well.[4] The frequency of methylphenidate use amongst undergraduate medical students varies widely. Jain et al[17] reported that 24.5% of non-medical methylphenidate users used it on a daily basis whereas Retief et al[8] found that only 5% of users used it in the week of their data collection. 85% of lifetime users have however used it in the year prior to the survey.[8] This confirms the findings of Steyn[6] and Teter et al[19] that students use methylphenidate sporadically and mainly during periods of high academic stress.

However, the use of psychostimulants for purposes other than the registered indications and without prescription, regular evaluation and follow-up may have serious adverse health consequences, especially if comorbid conditions (known or unknown) are present in individuals.

Methylphenidate causes a modest increase in average blood pressure and heart rate, although there is a wide inter-individual variation in response.[1] Even slight changes in baseline heart rate and blood pressure may cause significant morbidity or even mortality in individuals with ventricular arrhythmias, ischaemic heart disease or hypertension.[1] Long-term side effects in the adult population have not been fully evaluated, but individual case reports have shown an association with myocardial ischaemia[21] and increased risk for sudden cardiac death[22]. It is advised that baseline blood pressure and heart rate be measured prior to initiation of methylphenidate therapy, with dose increases and periodically during therapy.[1]

Psychiatric side effects include irritability, anxiety, tics and psychosis.[1] The risk for new onset psychosis attributed to methylphenidate is 0.1%.[23],[24] Severe depression may also ensue upon sudden discontinuation.[1] This is especially relevant in the student population as the majority use it only during high stress periods, such as exams.[17]

Other less serious side effects include gastrointestinal discomfort, dry mouth, insomnia and anorexia.[1]

Furthermore methylphenidate has a high potential for dependence. Physical dependence is not common at usual therapeutic doses, but psychological dependence may develop with long term use.[1],[4] This could be understood by the effect on the neurotransmitters – especially dopamine. The reward centres of the brain are innervated by dopaminergic neurons and account for the mild euphoria caused by methylphenidate.[4] Other psychostimulants such as amphetamines and cocaine may however exert physical dependence.[1] Intranasal methylphenidate has similar receptor effects to cocaine[25] and the risk for addiction is markedly increased if it is used via this route.

The question how methylphenidate is acquired then arises. In a study[8] on a sample of undergraduate medical students at a single South African university published in 2016 44% of participants received psychostimulants (such as methylphenidate) free from a friend or classmate. It was bought from a friend or classmate by 9% of participants and in 37% it was bought from another source (either online, a pharmacy or over the internet) with or without prescription. It was obtained from a family member with ADHD in 9% of cases and the rest did not answer where they sourced it from.[8]

In contrary Jain et al reported in 2017 that 70.6% of undergraduate medical students at the University of the Free State using methylphenidate obtained it with a valid prescription from a medical doctor. However, less than a third of these users have been diagnosed with ADHD.[17]

Overall this literature review has illustrated that the use of methylphenidate for non-medical purposes, including cognitive enhancement, is rife in undergraduate university students. Furthermore there are numerous physical and psychological risks attached to the use of methylphenidate without clear evidence of cognitive enhancement.

To our knowledge there are no studies which have previously examined the extent of use of methylphenidate in postgraduate medical students. Therefore the focus of this research

project was to determine the prevalence of the use of methylphenidate by Master of Medicine (MMed) students registered at the University of Stellenbosch.

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CHAPTER 4

Methodology

Study design

This was a descriptive cross sectional study.

Study setting/site

This was an anonymous online survey sent to the study population via email.

Study population

The target population were all students registered for the MMed programme at the Faculty of Health Sciences of the University of Stellenbosch at the time of conduction of the survey. There was no differentiation between students who have written the part one or intermediate College of Medicine examinations prior to registering as an MMed student. There was also no differentiation between any students who have failed any of the College of Medicine or MMed university examinations.

The number of MMed students registered is dynamic as the registration as a student is for the duration of employment as a registrar by the Provincial Administration of the Western Cape (PAWC) or National Health Laboratory Services (NHLS). Appointment by PAWC or NHLS can start at any time of the year and does not necessarily start or end at the normal university academic calendar year. There were 505 MMed students registered at the time of conducting this survey.

Sample

No sample selection was required as all registered MMed students were invited to participate in the survey.

Inclusion criteria

All students registered for the MMed programme at the Faculty of Medical and Health Sciences of the University of Stellenbosch were invited to take part in the survey.

Exclusion criteria

There were no exclusion criteria

Recruitment strategy

All registered MMed students received an email with a link to the electronic survey. The link was active from 1-27 September 2020. Students received a reminder to participate on a weekly basis if they have not responded.

Data collection and data management

Data were collected via anonymous participation in an online survey. A link to the survey was emailed to all students registered as MMed students at the Faculty of Medical and Health Sciences of the University of Stellenbosch.

The questionnaire utilised was newly designed and has not been validated. No validated questionnaire exists as the prevalence of methylphenidate use by post-graduate students has never been investigated. The questions were set by the primary investigator with assistance from the supervisor and flows from the literature review that was done.

The questionnaire has been compiled using the REDcap Consortium (Research Data Electronic Capturing Consortium) system. REDCap is a free, secure, web-based application designed by researchers to support data capture for research studies. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. REDCap servers are housed at the University of Missouri– Kansas City and all information is encrypted. Stellenbosch University is a registered consortium partner (www.project-redcap.org).

The survey was conducted electronically and anonymously and the captured database was structured in such a manner that the identity of the respondents could not be determined from the data captured. The only demographic data acquired were gender, age range and year of specialization. No reference to field of specialization was made as there are some departments that have very few MMed students registered.
See appendix E for questionnaire.

Data analysis plan

Data was exported from REDCap. Statistical analysis was conducted using Stata version 16.

Categorical variables were summarized by count (percentage). Continuous variables were summarized with mean (standard deviation) or median (interquartile range) depending on the distribution. We report prevalence by point estimate with the corresponding 95% confidence interval.

Test association on use and demographics were reported on using logistical regression models with a p-value of <0.05 considered as statistically significant.

Ethical considerations

Approval by regulatory authorities

Research was conducted in accordance with the Declaration of Helsinki and the Department of Health Guidelines for Good Clinical Practice.

Ethical approval was obtained from the University of Stellenbosch Health Research Ethics Committee (S20/03/068).

Institutional permission from Stellenbosch University's Division for Information Governance (DIG) was also be obtained prior to data collection. (IRPSD-1844)

Informed consent

In the emailed invitation, potential participants were informed of the purpose of the study, that it is completely anonymous, and that it has been approved by both the HREC of Stellenbosch University and Stellenbosch University's Division for Information Governance. By responding to the questionnaire, the participant granted consent that his/her responses be used for the purposes of the study. A copy of the email invitation can be seen in Appendix C.

Risks and benefits to participants

There was no physical risk to participants. Electronic data were completely anonymous and encrypted and there was no possible way of identification.

At the end of the survey participants were supplied with an electronic information sheet on the use of methylphenidate for non-medical purposes. (Appendix E). This addressed possible misconceptions with regards to the physical risk, danger and the abuse potential of methylphenidate.

CHAPTER 5

Author guidelines for journal submission

Specific guidelines to BMJ Postgraduate Medical Journal:

Articles should be presented in a way that is accessible to readers of a general medical journal. All research papers involving human subjects MUST contain a statement about ethics committee approval. Reports of randomised controlled trials should follow the revised CONSORT statement (Consolidated Standards of Reporting Trials.) published in JAMA (2001;285:1987-91), as closely as possible. See RCTs for more guidelines.
Papers should also summarise in list form "What is already known on the subject" and the study's main messages.
Word count: up to 3000 words

Abstract: Abstracts of up to 250 words are required for all original articles. Headings for experimental or observational studies should include: purpose of the study, study design, results and conclusions.
Tables/Illustrations: up to 6
References: up to 30

General guidelines applicable to all BMJ publications

Title page

The title page must contain the following information:

- Title of the article
- Full name, postal address and e-mail of the corresponding author
- Full name, department, institution, city and country of all co-authors
- Word count, excluding title page, abstract, references, figures and tables

Keywords

Authors can usually opt to (or are required to) choose keywords relevant to the content of the manuscript during the submission process. This assists in the identification of the most suitable reviewers for the manuscript. The selected keywords should also be included in the abstract itself.

Authors and Institutions

On submission of your article through our submission system you will be asked to provide a name, email address and institutional affiliation for all contributing authors. In the final published article author names, institutions and addresses will be taken from these completed fields and not from the submitted Word document.

Manuscript format

The manuscript must be submitted as a Word document. PDF is not accepted.

The manuscript should be presented in the following order:

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- **Preprints:** Rostami A, Sepidarkish M, Leeflang M, et al. First snap-shot meta-analysis to estimate the prevalence of serum antibodies to SARS-CoV-2 in humans. MedRxiv 20185017 [Preprint]. September 02, 2020 [cited 2020 Sep 20] https://doi.org/10.1101/2020.08.31.20185017.

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- **Law references:** The two main series of law reports, Weekly Law Reports (WLR) and All England Law Reports (All ER) have three volumes a year e.g. Robertson v Post Office [1974] 1 WLR 1176

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CHAPTER 6

Article published in BMJ Postgraduate Journal

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Prevalence of methylphenidate use by Master of Medicine students at a South African university

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ABSTRACT

Background Methylphenidate is mainly used for the treatment of attention-deficit/hyperactive-disorder (ADHD). Its effect of increased attentiveness leads to the potential of off-label use by students for academic enhancement—previously demonstrated in undergraduate students. No publication exists on postgraduate student use of methylphenidate.

Objectives To provide a summary of the self-reported prevalence and correlates of methylphenidate use in Masters of Medicine (MMed) students registered at the Faculty of Medical and Health Sciences of a South African university.

Methods A cross-sectional study was conducted. Data were collected via a self-administered anonymous online questionnaire distributed by email to 505 registered MMed students.

Results Of the 253 responses (response rate 50.1%) received 71 (28.1%) have used methylphenidate. Only 2.4% have been diagnosed with ADHD. The majority (73.2%) obtained it without a formal medical consultation. Self-prescription (26.8%) and prescription by a colleague without consultation (23.9%) contributed significantly. Academic performance enhancement was the primary motivation for use in 71.8% and 42.3% of users started using methylphenidate while registered as an MMed student. There was no statistically significant difference in terms of gender (p=0.151), age (p=0.288) or year of study (p=0.149).

Conclusions Off-label use of methylphenidate is prevalent in MMed students registered at this South African university. The prevalence is significantly higher than in undergraduate medical students. The non-conventional means of access is of great concern. Efforts should be made to discourage self-prescription, educate students on the dangers of methylphenidate use, promote better access regulation and enhance psychological support.

INTRODUCTION

Methylphenidate is classified as a central nervous system stimulant and is chiefly used in the management of attention-deficit/hyperactivity disorder (ADHD).[1] Clinically, the desired effects are decreased hyperactivity and distractibility, increased attentiveness and reduced impulsivity.[2 3] Mild euphoria, a decreased sense of fatigue as well as an increased completion of tasks are associated benefits.[2] These clinical effects have been shown to improve cognition if there is pathology rendering it suboptimal.[4] The effect of increased attentiveness and ability to concentrate leads to the potential of methylphenidate being used for off-label purposes. Students use it mainly for academic purposes, especially during periods of high academic stress.[5] 'Academic purposes' as noted here, alludes to the attempt at an increase in concentration, attention and alertness, with a hopeful improvement in academic performance while combating mental fatigue.

Current literature is inconclusive on whether psychostimulants, such as methylphenidate improves cognition in healthy individuals and suggests that the subjective impression that cognition is improved should rather be attributed to a feeling of well-being or euphoria being induced.[4 6]

The prevalence of ADHD in the general adult population is 2.5%, yet methylphenidate use by university students for off-label purposes is widely reported in international and South African literature with self-reported lifetime prevalence of psychostimulant use ranging from 5% to 35%.[7–17] No investigation on the prevalence of methylphenidate use among postgraduate students has been previously published.

Jain *et al* and Retief and Verster recently evaluated the self-reported use of psychostimulants by undergraduate medical students at South African universities. Jain *et al* found that the prevalence of methylphenidate use was 11% while Retief and Verster concluded that 18% had a lifetime prevalence of psychostimulant (including methylphenidate, dextroamphetamine, pemoline and modafinil) use.[12 14]

Generally considered a safe drug, methylphenidate causes a modest increase in average blood pressure and heart rate, although there is a wide inter-individual variation in response.[2] Even slight changes in baseline heart rate and blood pressure may cause significant morbidity or even mortality in individuals with ventricular arrhythmias, ischaemic heart disease or hypertension.[2] Long-term side effects in the adult population have not been fully evaluated, but individual case reports have shown an association with myocardial ischaemia and increased risk for sudden cardiac death.[18 19] It is advised that baseline blood pressure and heart rate be measured prior to initiation of methylphenidate therapy, with dose increases and periodically during therapy.[2]

Psychiatric side effects include irritability, anxiety, tics and psychosis.[2] Severe depression may also ensue on sudden discontinuation.[2] This is especially relevant in the student population as the majority use it only during high-stress periods, such as examinations.[12] Furthermore methylphenidate has a high potential for dependence. Physical dependence is not common at usual therapeutic

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doses, but psychological dependence may develop with long-term use.[2 3]

The present research aims to investigate the prevalence of methylphenidate use, but also attempts to gain insight into the means of access and motivation for its use.

OBJECTIVES

The objective of this study was to provide a summary of the self-reported prevalence and correlates of methylphenidate use by Masters of Medicine (MMed) students registered at the Faculty of Medical and Health Sciences at a South African university.

METHODS

Study design and setting

A cross-sectional study was performed using an anonymous online survey tool.

Study population

The target population included all students, across all specialties, registered for the MMed programme at the Faculty of Health Sciences at a South African university. All MMed students are qualified medical practitioners studying towards qualifying as a specialist in various medical fields. Trainees are required to be registered as MMed students for four or 5 years depending on the field of specialisation. Various sittings of formal theoretical, oral and clinical examinations must be completed successfully before registration as specialist may ensue. There were no exclusion criteria. At the time of conducting the research there were 505 registered MMed students.

Questionnaire

The authors designed a literature directed questionnaire as no validated instrument to measure methylphenidate use exists. The questionnaire was designed on the REDCap Consortium (Research Data Electronic Capturing Consortium) system. Limited demographic data (gender, year of study and age category) were collected to ensure anonymity. The questionnaire included questions pertaining to use of methylphenidate, index period of use, frequency of use, primary and secondary purpose for use, ADHD diagnosis, method of obtaining methylphenidate and side-effects experienced. Many questions required a single most applicable answer, while other allowed for ranking of preferences. Participants could elaborate if 'other' was selected as an option.

Data collection

A link to the anonymous, self-administered questionnaire was emailed to all registered MMed students. Data collection took place from 1 to 27 September 2020. After the initial invitation weekly reminders were sent to all registered students for 3 weeks. The anonymous responses were securely stored on the REDCap system.

Statistical analysis

Data were exported from REDCap to Microsoft Excel. Statistical analysis was done using Stata V.16. Categorical variables were summarised by count (percentage). Continuous variables were summarised with mean (SD). We report prevalence by point estimate with the corresponding 95% CI. Test associations on demographics were reported on using logistical regression models with a p value of <0.05 considered as statistically significant.

RESULTS

Demographic data

The electronic questionnaire was distributed to the 505 registered MMed students at a single South African university. The response rate was 50.1% with 253 completed questionnaires. Of these 118 (46.6%) were male and 135 (53.4%) were female. The highest percentage of respondents was from students in their fourth year of study (24.9%) and in the age group 30–35 years old (68.4%). Table 1 highlights the demographics of the respondents.

Prevalence and ADHD diagnosis

Overall, 28.1% (n=71; 95% CI 22.52 to 33.60) of respondents reported having used methylphenidate while only 2.4% (n=6) have been formally diagnosed with ADHD. A further 11.7% think that they may potentially have ADHD, but have not been diagnosed. More than half of the respondents (n=135; 53.4%, 95% CI 47.2 to 59.5) know of an MMed registered student using methylphenidate for academic purposes. The study

Table 1 Demographic data of respondents

	Total respondents		Response rate*	MPH used		MPH not used		
	n	%	%	n	%	n	%	P value
Gender								0.151
Male	118	46.6	45.7	28	23.7	90	76.3	
Female	135	53.4	54.7	43	31.9	92	68.1	
Year of study								0.149
Year 1	57	22.5	51.8	10	17.5	47	82.5	
Year 2	44	17.4	52.4	17	38.6	27	61.4	
Year 3	56	22.1	69.1	15	26.8	41	73.2	
Year 4	63	24.9	63.0	17	27.0	46	73.0	
Year 5	33	13.0	25.4	12	36.4	21	63.6	
Age category								0.288
<30	20	7.9	50.0	4	20.0	16	80.0	
30–35	173	68.4	59.0	55	31.8	118	68.2	
36–40	50	19.8	36.8	10	20.0	40	80.0	
>40	10	4.0	25.6	2	20.0	8	80.0	

*Response rate refers to the percentage of the demographic category that responded to the survey.
MPH, methylphenidate.

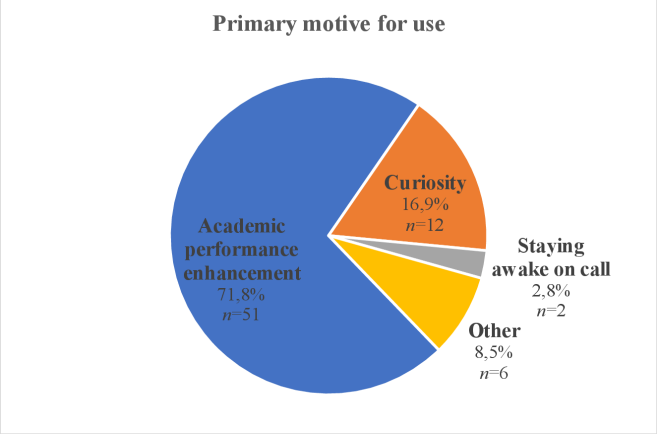

Figure 1 Primary motive for methylphenidate use.

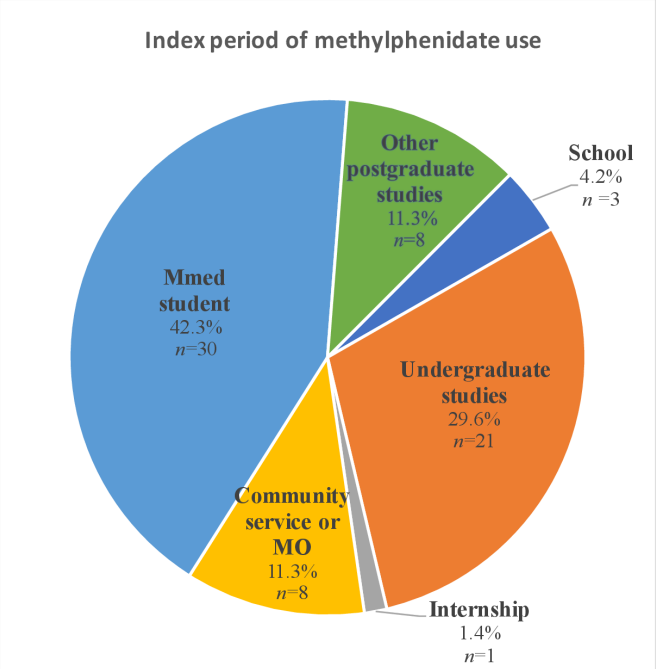

Figure 2 Index period of methylphenidate use. MO, Medical Officer

cohort correlated well to the population investigated. There was no statistically significant difference (p=0.151) between male (n=28; 39.4%) and female (n=43; 60.6%) respondents using methylphenidate. We were unable to demonstrate any statistically significant difference (p=0.288) in usage among different age categories (<30 n=4; 5.6%, 30–35 n=55; 77.5% 36–40 n=10; 14.1%,>40 n=2; 2.8%). We were also unable to demonstrate any statistically significant difference (p=0.149) in usage among students in different years of study (year 1 n=10; 14.1%year 2 n=17; 23.9%year 3 n=15; 21.1%year 4 n=17; 23.9%year 5 n=12; 16.9%).

Use for postgraduate academic purposes

More than a fifth (21.3%; n=54) of respondents to the questionnaire have used methylphenidate while being registered as an MMed student. Improvement of academic performance (71.8%) was the most common primary reason for using methylphenidate, followed by curiosity (16.9%)—indicated in figure 1. More than three quarters (76.1%, 95%CI 66.13 to 85.98; n=54) of lifetime methylphenidate users used it while being registered as an MMed student with nearly half (45.1%; n=32) using it in the year leading up to data collection. Figure 2 indicates the index period of use for 42.3% (n=30) was while being registered as an MMed student whereas 29.58% (n=21) started while being undergraduate students and only 3 (4.2%) while at school.

Frequency of use

Methylphenidate was used sporadically by 32.4% (n=23) of users while 23.9% (n=17) used it daily. Less than a third (29.6%) of life-time users used it once-off only. The rest of the users used it once per week (8.5%), once per month (4.2%) or once per year (1.4%).

How methylphenidate was obtained

Figure 3 indicates that methylphenidate was prescribed by a general medical practitioner or specialist to 26.8% (n=19) after a consultation. Equal numbers of participants report self-prescription. A prescription for methylphenidate was obtained from a colleague without a formal consultation by 23.9% (n=17) while 19.7% (n=14) received the medication from a friend or colleague to whom it was legally prescribed.

Side-effects and risk

More than two-thirds (70.4%, n=50) of users reported side-effects with insomnia (35.2%), anxiety (33.8%) and palpitations (32.4%) most frequently occurring. Withdrawal symptoms developed in six (8.5%) respondents on discontinuing methylphenidate. The majority (71.2%, n=180) of all respondents believed that methylphenidate use has both physical and psychiatric risk. Much smaller groups believed that there is no risk at all (9.9%, n=25), risk isolated to mental health (11.9%, n=30) and risk limited to physical health (7.1%, n=18).

DISCUSSION

In this cohort methylphenidate had a lifetime prevalence of 28.1% with more than a fifth of respondents using it while being registered as an MMed student. The prevalence of use in our population is much higher than reported in undergraduate South African medical students or in international students.[9–12 14] In our study population only 9.5% of users started using methylphenidate during or prior to their undergraduate medical studies. However, 42.3% started using methylphenidate for the first time while being registered as an MMed student.

We conclude that off-label use is rife in our study population as the prevalence is 11.7-fold higher than the diagnosis of ADHD.

Numerous factors could contribute to the increased prevalence of use in MMed students. Ease of access is one of these. Self-prescription and prescription by a friend or colleague without consultation contributed significantly to the manner in which methylphenidate was obtained. Undergraduate medical students would not be able to obtain methylphenidate in this manner. Jain *et al* reported in 2017 that 70.6% of undergraduate medical students at the University of the Free State obtained it with a valid prescription after consulting a medical doctor.[12] In contrary only 26.8% of users in our population obtained it after formally consulting a general medical practitioner or specialist.

Methylphenidate, a schedule 6 drug, is generally considered a safe drug, but its use for purposes other than the registered indications, regular evaluation and follow-up may have serious adverse health consequences, especially if comorbid conditions (known or unknown) are present in individuals. The risk of sudden cardiac death or ventricular arrhythmia is close to

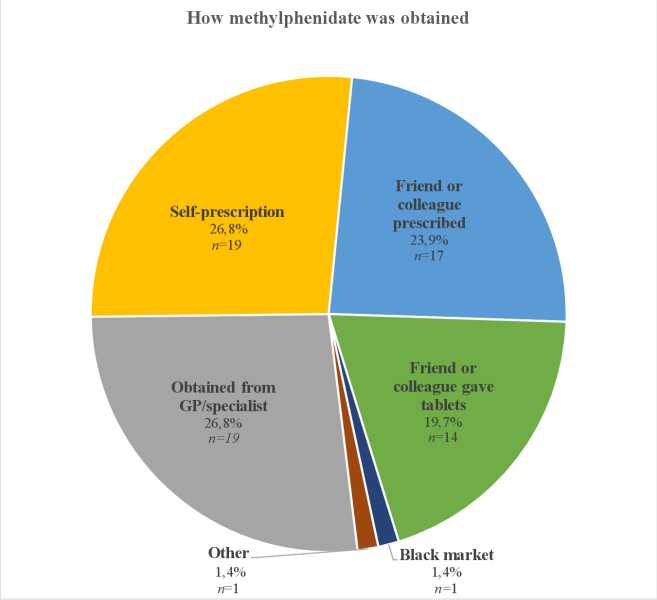

Figure 3 How methylphenidate was obtained. GP, general practitioner.

double after methylphenidate initiation in adults.[19] Development of psychosis has also been reported.[2] The vast majority of respondents admitted to knowing that methylphenidate use may have both physical and psychiatric risks. It is thus worrisome that almost three-quarters of users obtained it without a medical consultation. Being a schedule 6 drug methylphenidate should be a highly controlled substance. The authors found the ease of access concerning and believe it warrants the necessary attention of the relevant authoritative bodies and regulatory agents.

The authors postulate that the high prevalence of methylphenidate use in this cohort is linked to the perception that MMed students have tremendous stress and pressure compounded by occupational and academic demand. This is supported by the sporadic use of methylphenidate during times of academic pressure by a third of users, the primary purpose of use being academic performance enhancement and that 42.3% of users in our population started using methylphenidate specifically for MMed academic purposes. This is indicative of the perceived benefit of methylphenidate to aid with cognitive function. However, current literature is inconclusive as to whether methylphenidate objectively improves cognition in healthy individuals and suggests that the subjective impression that cognition is improved should rather be attributed to the feeling of euphoria or well-being being induced.[4 6] Students using methylphenidate may therefore expose themselves to serious potential adverse effects without any true benefit.

The perception of high pressure and demand on MMed students is supported by the reported prevalence of burnout among MMed students. Two South African studies have shown that the level of burnout in MMed students is higher than doctors who have not started specialising or have completed specialising and are working in similar environments.[20 21] One South African university reported a burnout prevalence of 84% in their MMed population.[22] Burnout leads to the reduction in ability to concentrate and students may attempt to pharmaceutically correct this. Although this cannot be directly extrapolated to our study population, it may be an indicator of a possible motive for using methylphenidate. Methylphenidate may however contribute to burnout by means of side-effects experienced. Insomnia occurs in more than a third of our cohort of methylphenidate users—exaggerating the subjective feeling of exhaustion and depleted energy levels and in effect contributing to the development of burnout in the predisposed individual.

Potential harm in the light of minimal evidence for cognitive benefit in healthy subjects places the user at risk while the prescriber is at medicolegal risk. This is even more true in the event of off-label prescription after consultation and prescription without a formal consultation—both frequent occurrences in our cohort. Professionalism of the prescriber may be in question. In traditional medicine off-label prescription for the treatment of disease would not be considered unethical although off-label prescription for the purpose of enhancement in the absence of disease may well be. Performance enhancement in sport as an example is globally prohibited—not only is it unethical, but also illegal. Morally it would be difficult to justify an attempt to enhance cognition in the student population where cognitive benefit is questionable and safety is not established. Future large randomised control trials should shed light on current lacking evidence, but until then the authors believe that the prescription of methylphenidate for performance enhancement, although not illegal, is not ethically justifiable.

Study limitations

Study limitations include the use of a non-validated self-administered questionnaire. Selective non-disclosure or dishonesty due to the sensitive nature of the topic could have affected the quality of the data. The data were collected at a single university and should not be extrapolated to other universities or fields of study.

CONCLUSION

This research demonstrates that the prevalence of methylphenidate use in our population is much higher than reported in undergraduate medical students and nearly 12 times higher than the prevalence of diagnosed ADHD. Academic performance enhancement is the most common primary reason for its

Main messages

- Methylphenidate use in MMed students is highly prevalent.
- Academic performance enhancement is the most common primary purpose for use.
- Acquisition is predominantly by non-conventional means.

Current research questions

- Is the prevalence in our cohort different to other postgraduate populations or is this a global phenomenon?
- Is there any objectively measurable cognitive benefit in students using methylphenidate compared with non-users?
- What is the incidence of serious adverse events attributable to methylphenidate in the student population?

What is already known on the subject

- Undergraduate student use of methylphenidate has been extensively researched with varying prevalence reported.
- Postgraduate student use is not reported on previously.

use and acquisition is predominantly without a formal medical consultation. This is of great concern as methylphenidate is a schedule 6 pharmacological agent and should be highly regulated, not to mention the potential health consequences to the unmonitored user. We postulate that a combination of ease of access, added academic and work pressure and a high degree of burnout may contribute to the identified phenomenon. Efforts should be made to promote awareness of potential harm of methylphenidate with minimal evidence for cognitive benefit in healthy students, discourage self-prescription, increase access and knowledge of available psychological support to students in need and to develop interventions to limit non-conventional means of access.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was obtained from the Health and Research Ethics Committee of the University of Stellenbosch (ref. no. S20/03/068). Institutional permission, to conduct research on registered students, was received from the Division of Institutional Governance of the University of Stellenbosch (ref. no. IRPSD-1844).

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CHAPTER 7

Appedixes

Appendix A: Ethical approval

UNIVERSITEIT
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Approval Notice

New Application

08/07/2020

Project ID :14705

HREC Reference No: S20/03/068

Project Title: The self-reported prevalence of methylphenidate use by Master of Medicine (MMed) students registered at the Faculty of Medicine and Health Sciences at the University of Stellenbosch

Dear Dr Willem Louw

The **New Application** received on 18/06/2020 14:49 was reviewed by members of **Health Research Ethics Committee** via **expedited** review procedures on 24/06/2020 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Date: 24 June 2020

Protocol Expiry Date: 23 June 2021

Please remember to use your Project ID 14705 and Ethics Reference Number S20/03/068 on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Translation of the informed consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/14705

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mrs. Ashleen Fortuin
Health Research Ethics Committee 1 (HREC1)

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)•REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372

Appendix B: Institutional permission from University of Stellenbosch

UNIVERSITEIT • STELLENBOSCH • UNIVERSITY
jou kennisvennoot • your knowledge partner

INSTITUTIONAL PERMISSION:

AGREEMENT ON USE OF PERSONAL INFORMATION IN RESEARCH

Name of Researcher: Dr Willem Louw

Name of Research Project: The self-reported prevalence of methylphenidate use by Master of Medicine (MMed) students registered at the Faculty of Medicine and Health Sciences at the University of Stellenbosch

Service Desk ID: IRPSD-1844

Date of Issue: 19 August 2020

The researcher has received institutional permission to proceed with this project as stipulated in the institutional permission application and within the conditions set out in this agreement.

1 WHAT THIS AGREEMENT IS ABOUT	
What is POPI?	1.1 POPI is the Protection of Personal Information Act 4 of 2013. 1.2 POPI regulates the entire information life cycle from collection, through use and storage and even the destruction of personal information.
Why is this important to us?	1.3 Even though POPI is important, it is not the primary motivation for this agreement. The privacy of our students and employees are important to us. We want to ensure that no research project poses any risks to their privacy. 1.4 However, you are required to familiarise yourself with, and comply with POPI in its entirety.
What is considered to be personal information?	1.5 'Personal information' means information relating to an identifiable, living, individual or company, including, but not limited to: 1.5.1 information relating to the race, gender, sex, pregnancy, marital status, national, ethnic or social origin, colour, sexual orientation, age, physical or mental health, well-being, disability, religion, conscience, belief, culture, language and birth of the person; 1.5.2 information relating to the education or the medical, financial, criminal or

Appendix C: Participant invitational email

Dear MMed student

Your participation in the attached survey will be greatly appreciated!

- It forms part of the research component in acquiring the degree MMed (Anes) of Willem Louw.
- The survey will take you less than 10 minutes to complete.
- Your participation is completely voluntary and can be terminated at any point

Rationale

The survey aims to establish the prevalence of Methylphenidate (e.g. Ritalin, Concerta) use by MMed students registered at the University of Stellenbosch.

Methylphenidate is mainly used for the treatment of Attention Deficit Hyperactive Syndrome (ADHD). It has been shown throughout the South African and international literature that the self-reported prevalence of methylphenidate use by undergraduate university students is significantly higher than the prevalence of ADHD. The prevalence of methylphenidate use by postgraduate students is not researched to date. The use of Methylphenidate is not without risks and may have various life-threatening side-effects. The investigators find it necessary to establish the prevalence of methylphenidate use by MMed students and to educate the study population of its risks.

The survey

The survey will be completely anonymous. Data will be hosted and encrypted using the REDCap Consortium web-based system. No link between participant and response to the survey will be possible, not even by the researcher.

All MMed students at the FMHS at the University of Stellenbosch will receive invitations to participate.

By completing the survey, you grant permission that your response may be used as part of the research.

If you wish to partake in the lucky draw you will be requested to provide an email address. This identification will be completely detached from your response assuring anonymity of response.

Ethics

The research has received approval from the Health Research Ethical Committee (HREC) of the University of Stellenbosch (S20/03/068) and from the Division of Information Governance (DIG) of the University of Stellenbosch.

The study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, and the Department of Health Ethics in Health Research: Principles, Processes and Studies (2015).

You can phone the Health Research Ethics Committee at 021 938 9677/9819 if there still is something that concerns you about how this study is being conducted, or if you have a complaint.

Dissemination

Should the results of this research be of significance in comparison to already published research it will be summarized in a research article submitted to a scientific journal.

Should the research article not be accepted by journals the article will nevertheless be made available to the heads of departments of the Faculty of Medical and Health Sciences for distribution to members of its department.

Contact details

Primary Investigator: Willem Louw wanlouw@gmail.com 084 626 2974
Supervisor: Ryan Davids darvyan@gmail.com
HREC: 021 938 9677/9819

Thank you very much for your assistance!

Willem Louw

Appendix D: Questionnaire

Methylphenidate use in MMed students

Please complete the survey below with regards to your use of Methylphenidate (Ritalin, Concerta etc)

Thank you very much!

Regards

Willem Louw

What is your gender?	◯ Male ◯ Female
What is your year of study?	◯ Year 1 ◯ Year 2 ◯ Year 3 ◯ Year 4 ◯ Year 5 or more
What is your age?	◯ Younger than 30 ◯ 30 - 35 ◯ 36-40 ◯ Older than 40
Have you ever been diagnosed with Attention-deficit-hyperactive syndrome (ADHD)?	◯ Yes ◯ No
Do you think you may suffer from ADHD, but have not been diagnosed?	◯ Yes ◯ No
Do you know any MMed student using Ritalin/Concerta or other formulations of methylphenidate for purposes of studying or improving academic performance?	◯ Yes ◯ No
Have you ever used Ritalin/Concerta/another formulation of Methylphenidate, even once in your life?	◯ Yes ◯ No
Have you used Ritalin/Concerta/another formulation of Methylphenidate in the past year?	◯ Yes ◯ No

When was the first time you used Ritalin/Concerta/another formulation of Methylphenidate?

- ◯ School
- ◯ Undergraduate studies
- ◯ Internship
- ◯ Community Service MO or MO
- ◯ MMed studies
- ◯ Other postgraduate studies

Have you used Ritalin/Concerta/another formulation of Methylphenidate while studying for any CMSA specialist exam (part one, intermediate or part two) or for any academic purpose towards specialising?

- ◯ Yes
- ◯ No

How frequently do/did you use Ritalin/Concerta/another formulation of Methylphenidate?

- ◯ Sporadically
- ◯ Daily
- ◯ Once per week
- ◯ Once per month
- ◯ Once a year
- ◯ Once off

What is/was the main reason you used Ritalin/Concerta/another formulation of Methylphenidate?

- ◯ Improve academic performance
- ◯ Staying awake on call
- ◯ Recreational purposes
- ◯ Weight loss
- ◯ Curiosity
- ◯ Other

Please specify other

_____

Are there additional reasons you use/have used Ritalin/Concerta/another formulation of Methylphenidate for?

- ☐ No
- ☐ Improve academic performance
- ☐ Staying awake on call
- ☐ Recreational purposes
- ☐ Weight loss
- ☐ Curiosity
- ☐ Other

Please specify other

_____

By what route of administration do/did you use Ritalin/Concerta/another formulation of Methylphenidate?

- ☐ Oral
- ☐ Intranasal
- ☐ Intravenous
- ☐ Other

Please specify other

_____

How do/did you obtain Ritalin/Concerta/another formulation of Methylphenidate?

- ◯ Colleague prescribe
- ◯ Self-prescription
- ◯ Prescribed by GP or specialist after a consult
- ◯ Black market
- ◯ Obtained from someone who was legally prescribed it (e.g. a friend)
- ◯ Other

(Mainly, if in more than one way)

Please specify other	_____
Did you experience any side-effects?	☐ Palpitations ☐ Anxiety ☐ Irritability ☐ Insomnia ☐ Decreased appetite/weight loss ☐ Withdrawal upon discontinuation (e.g. depressed mood) ☐ other ☐ none
Please specify other	_____
Do you think using Methylphenidate	◯ provides an unfair academic advantage to the user? ◯ does not provide and unfair academic advantage to the user?
Do you think there are	◯ physical risk to the use of methylphenidate? ◯ psychiatric risk to the use of methylphenidate? ◯ both physical and psychiatric risk to the use of methylphenidate? ◯ no physical or psychiatric risk to the use of methylphenidate?

Appendix E: Information sheet to participants after survey submission

INFORMATION SHEET:

Do you or have you used METHYLPHENIDATE?

Indications for methylphenidate(Ritalin, Concerta etc) use include ADHD, narcolepsy, refractory major depression.

5 – 35% of University students globally have admitted to using the product to enhance cognition for academic purposes.

Will it help me study?

Literature is inconclusive on whether it improves cognition in users without ADHD.
Reports show no change in visual memory and equivocal reports on enhanced learning.

Surely I can't get addicted to Methylphenidate…right?

Wrong! Psychological dependence can occur with long term use and even has potential for other side effects such as :
new onset psychosis (seen in 1:1000)
Increase in baseline **blood pressure and heart rate** which may lead to severe **morbidity and mortality** (in underlying hypertension, ischaemic heart disease or ventricular arrythmias)

I think I have a problem:

Signs of Methylphenidacte dependence include:

- Anxiety / Depression / Panic attacks
- Asking other people for their tablets
- Tachycardia
- Decreased appetite
- Stealing, lying, doctor shopping
- Crushing and snorting Methylphenidate

ADHD helpline: 0800 55 44 33
Substance abuse line: 0800 11 12 13

For more information on Methylphenidate dependence visit:
https://americanaddictioncenters.org/ritalin/use-and-abuse

Appendix F: Turnitin report

accepted submission

ORIGINALITY REPORT

5%	3%	3%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

MATCH ALL SOURCES (ONLY SELECTED SOURCE PRINTED)

2%

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