Smart drug use in the Department of Anaesthesiology at the University of the Witwatersrand

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in the partial fulfilment of the requirements for the degree of

Master of Medicine in the branch of Anaesthesiology

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DECLARATION

I, Natasha Jurković, herewith declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signed

On this____21st_____day of_____September_____2021 at _____Johannesburg_____.

DEDICATION

This project is dedicated to Paula, Gabriele, Gianfranco, Katia and Kiara.

Without you, it could not have been done.

ABSTRACT

Background

Neurocognitive enhancement is an internationally occurring practice for which nootropics and prescription smart drugs are being used. It has been described in school-going children, undergraduate and postgraduate students, as well as in the work population.

Objectives

To qualitatively assess the practice of pharmacological cognitive enhancement within the Department of Anaesthesiology at the University of the Witwatersrand.

Methods

A peer-reviewed questionnaire was administered to the medical officers, registrars and consultants working in the Department of Anaesthesiology, to establish prevalence, substances used, motivators, routes of obtaining prescription nootropics, as well as the use of 'downers'.

Results

A total of 139 responses were received from a possible 208. Ninety percent of respondents drank coffee, but not to improve cognition. Other caffeinated drinks were consumed with the intention of enhancing neurocognition in 45% of cases. Non-caffeinated energy drinks were consumed in 73% of cases, predominantly to improve sports performance. The nootropics most commonly used included omega 3 (34%), ginkgo biloba (16%) and caffeine tablets (5%). Prescription nootropics were consumed by 25% of respondents. Prescription nootropics included methylphenidate (91.7%), modafinil (11.1%), atomoxetine (2.8%) and donepezil (2.8%). Increased concentration was the motivation in 69% of responses, 22% were using prescription nootropics to stay awake, 17% for work performance and 17% to experiment. Frequency of use was annual in 56% of cases. Daily use was quoted in 20% of responses. Examination time constituted 83% of prescription nootropic usage. Self-prescription was found in 31% of cases, with prescriptions obtained from colleagues or friends in 27%. Smart drug use was informed in 92% of cases. Internet sources were predominantly used (85%). The most common side effects reported included palpitations (47%), irritability (31%), agitation (28%) and headache (25%). In terms of substances used to relax, 55% of respondents had used a 'downer', 83% of which constituted alcohol, followed by sleeping tablets in 22% of cases.

Conclusion

This study shows that smart drug use for neurocognitive enhancement occurs in this department in proportions similar to those seen in international institutions. The substances used are also similar, although prescription nootropics differ in terms of those available in South Africa. Neurocognitive enhancement may be more widespread than this study has shown. Further investigation is necessary to quantify the practice in the South African context.

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To Dr Jonathan Kay and Dr Razeena Lockhat, thank you for all the support, patience and time to make this MMed possible.

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NOMENCLATURE

The following definitions are used in this study.

Anaesthetist: is any qualified doctor working in the Department of Anaesthesiology, including medical officers, registrars and consultants.

Intern: is a doctor who completed a university degree, but is currently undergoing practical training prior to registration as an independent practitioner with the Health Professionals Council of South Africa.

Medical officer: is a qualified doctor practising in the Department of Anaesthesiology under specialist supervision. This includes those performing community service. Medical officers with more than ten years of experience are career medical officers and are regarded as consultants.

Registrar: is a qualified doctor who is registered with the Health Professions Council of South Africa as a trainee anaesthetist.

Consultant: is a specialist anaesthesiologist or career medical officer.

Stimulant: any substance that results in sympathetic nervous system output.

"Downer" or depressant: any substance that increases parasympathetic nervous system output or dampens the sympathetic nervous system response.

Nootropic: any substance used to facilitate learning and improve memory. In this study, nootropics are limited to over-the-counter drugs used in this capacity.

Smart drugs or prescription nootropics: prescription drugs used for cognitive enhancement and found in the South African Medicines Formulary.

LIST OF ABBREVIATIONS

ADHD: attention deficit hyperactivity disorder

COMT: catechol-O-methyltransferase

STATEMENT

The formatting of this research report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the rest of the research report in order to comply with the author guidelines of the South African Medical Journal to which the article is intended to be submitted.

Draft Article

Smart drug use in the Department of Anaesthesiology at the University of the Witwatersrand

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Introduction

'Brain doping' entails the use of psychoactive drugs by healthy individuals in order to enhance neurocognition. This is also known as pharmacological neuroenhancement, cosmetic neurology, academic performance enhancement, academic or intellectual doping.[1] Cognitive functions that can be enhanced include attention, vigilance, concentration, memory and mood.[1, 2] Increasing academic and work demands provide a conducive environment for the use of stimulants and prescription drugs for cognitive enhancement. This trend has been noted in students at scholastic, undergraduate and postgraduate level. It has also been described in the work population.[3] The phenomenon initially surfaced in the United States of America, but has now been reported in various European countries, as well as Australia, New Zealand, and certain South American nations.[1, 4-9] Prevalence rates in the United States of America range from 8.1% to 27.6%, with a preponderance towards amphetamine-dextroamphetamine (Adderall) use.[6] Of these, lifetime use and past-year prevalence were found to be 8.3% and 5.9% respectively. In Europe, prevalence tends to be lower with rates of 0.78% in Germany to 6.2% in Switzerland, with methylphenidate as the common drug of choice.[1, 8, 10] Australian statistics show a prevalence between 1.4% and 4.4%.[9] New Zealand has a prevalence of 6.6%.[9]

Substances commonly associated with cognitive enhancement include over-the-counter stimulants (coffee, caffeinated energy drinks, caffeine tablets), nootropics (Ginkgo biloba, omega 3, piracetam, etc.), smart drugs or prescription nootropics (methylphenidate, amphetamines, modafinil, acetylcholinesterase inhibitors) and illicit drugs.[7] Nootropics were first described in 1972 based on the model drug, piracetam.[4] These were initially defined as non-toxic and safe psychotropic drugs activating brain mechanisms to compensate for central nervous system deficits, without induction of reticular, subcortical or limbic responses.[4] They also facilitate learning and improve memory.[4] In recent times, 'smart drugs' have become the descriptor for nootropics that are prescribed for certain neurological disorders, but used by healthy individuals in the pursuit of cognitive enhancement.[4]

Motivators underlying 'brain doping' include improving concentration (65.2%), assisted studying (59.8%), increasing alertness (47.5%), 'getting high' (31.0%) and experimentation (29.9%).[6, 11] Other reasons driving smart drug use are weight loss, improving performance in the face of sleep deprivation and customising sleep-wake cycles.[12] Use is usually increased in periods of heightened stress such as examinations. These motivators underlie an adaptive response to an ever increasing competitiveness in the academic and sociocultural spheres, demanding increased productivity. The medical field is one such field demanding rigorous work ethic and continued academic pursuit. The objective of this study is to describe the practice of neurocognitive enhancement within the Department of Anaesthesiology at the University of the Witwatersrand.

Methods

A prospective, descriptive, contextual, observational and qualitative research design was followed in this study. A multiple choice, paper-based questionnaire was designed based on the current literature and reviewed by three external consultants affiliated to the Department of Anaesthesiology, as well as an external public health specialist.

Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) [HREC Ref: R14/49] with the principles of the Declaration of Helsinki and the South African Guidelines for Good Clinical Practice adhered to throughout.[13, 14]

The questionnaire was distributed to consultants, registrars (junior and senior) and medical officers working in the department of Anaesthesiology at the University of the Witwatersrand, using a convenience sampling method. Interns were excluded from the study based on the brevity of time within the Department. Participation was voluntary and anonymous, the questionnaire being self-administered. The sample size was 208, comprising 22 medical officers, 112 registrars and 74 consultants. Data was collected from 15 May 2020 to 31 July 2020.

All data are categorical and summarised as counts and percentages. Fisher's Exact Test was used to assess whether there was a significant relationship between the outcome of the question of interest and age, gender and career seniority. The threshold for statistical significance was set at $p < 0.05$. All analysis were conducted using the R Statistical Environment (v4.0.2).

Results

A total of 139 responses were received out of the 208 questionnaires distributed (response rate 67%), with the majority of the cohort being between 31 to 40 years old (61%). Females made up 58% of the respondents, whilst 42% were male. The majority of the sample comprised senior staff (figure 1).

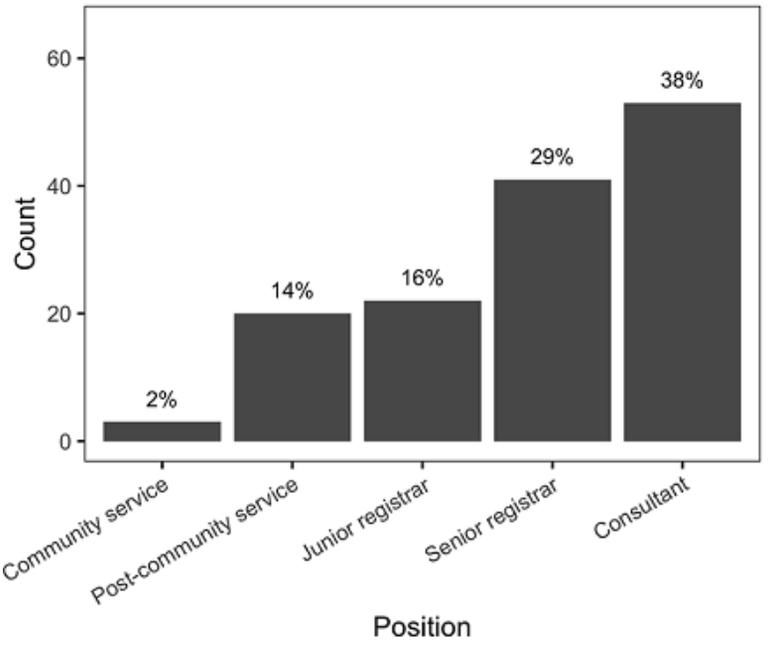

Figure 1 Distribution by position

Almost all respondents were non-smokers (93%). Of the ten respondents who did smoke, 40% did so daily, whilst 30% did so on a social basis. There was no significant association detected between smoking and gender (p=0.743), age (p=0.577) or seniority (p=0.300). Only two respondents smoked e-cigarettes.

Coffee was consumed by 90% of respondents of which 72% did so daily, whilst 18% drank coffee on a social basis. The most common reason cited for consumption was 'enjoyment of taste', whilst a third of respondents used coffee to 'stay awake' and one quarter consumed coffee to improve concentration. No association was detected between coffee consumption and seniority or gender, yet all respondents over the age of 40 years consumed coffee (p=0.024).

Other caffeinated drinks commonly consumed are shown in figure 2. Green tea was significantly associated with female gender, whilst males preferred Coca-Cola (p=0.014). These caffeinated drinks were consumed sporadically in most cases, as well as to maintain wakefulness (76%), improve concentration (41%) and work performance (21%). Sports performance was only quoted as motivation in 18% of cases.

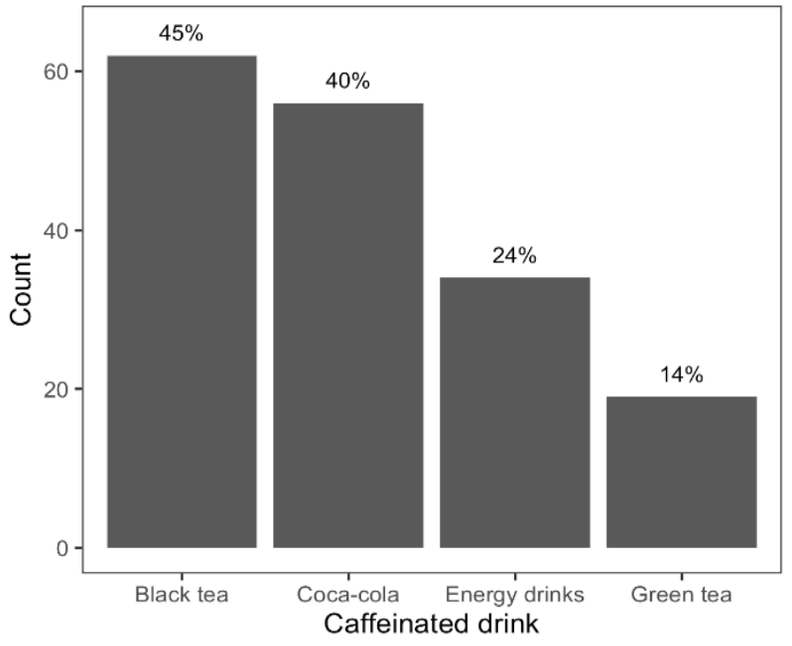

Figure 2 Caffeinated drinks

Non-caffeinated energy drinks were consumed in 73% of cases, for social reasons (45%) or sports performance (39%), with very few using these drinks to increase concentration (3%) or wakefulness (16%). There was, however, a significant association between non-caffeinated energy drink consumption and gender, such that males were more likely to consume these drinks (p=0.004). Respondents older than 40 years tended not to consume these drinks at all (p=0.018).

When considering knowledge regarding nootropics, 62% of respondents had heard of nootropics with no statistical difference regarding age (p=0.284), gender (p=0.223) or

seniority (p=0.127). Regarding neurocognitive enhancement, 70% of respondents were aware of the subject. Once again the study found no significant differences in age (p=0.577), gender (p=0.355) and seniority (p=0.883).

The nootropics most commonly used include omega-3 (34%), ginkgo biloba (16%) and caffeine tablets (5%). Twenty percent took these supplements daily, whilst 39% took them a few times a year. The remainder consumed nootropics sporadically. Consumption within the last 30 days was reported in 31%. Nootropic use was heavily weighted in the neurocognitive enhancement sphere, with 45% of use being during periods of study and 38% during periods of increased stress. There was no significant association between age (p=1), gender (p=0.866) or seniority (p=0.547) and nootropic use.

Prescription nootropics were consumed by 25% of respondents (figure 3). Of these, 38% constituted registrars and 26% consultants. Increased concentration was the motivation in 69% of participants, 22% were using prescription nootropics to stay awake, 17% for work performance and 17% to experiment. Only two respondents were using these medications because they had been prescribed. This correlated with the three individuals (2%) that had been previously diagnosed with attention deficit hyperactivity disorder (ADHD).

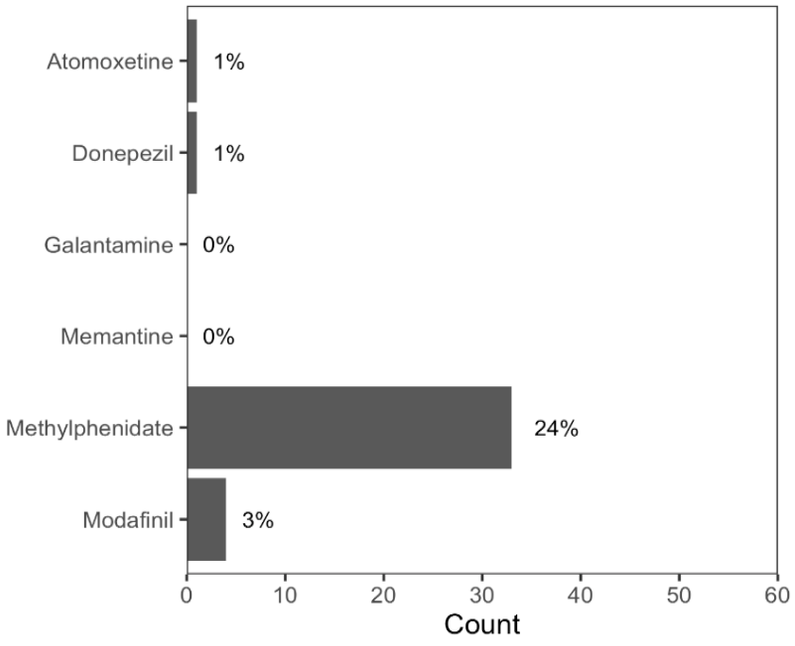

Figure 3 Prescription nootropics

Annual use of prescription nootropics was reported in 56% of cases, with a 20% rate of daily use. Despite this, when questioned on whether they had taken prescription nootropics in the last 30 days, only eight percent responded positively. The majority (83%) used prescription nootropics during examination time. All users took these medications orally, with only one respondent having done so intranasally.

Concerning the sourcing of prescription nootropics, 22% used loose tablets from friends or acquaintances, 28% had prescriptions written by friends, 31% self-prescribed and 25% had

prescriptions from a general practitioner or specialist. The latter, however, did not correspond with users who had been diagnosed with ADHD. Seven users indicated that they had used prescription nootropics previously at school or undergraduate level.

The majority of respondents (92%) researched the drugs prior to their use. Sources of information included the internet (85%), consultation with colleagues (64%) or the opinion of a general practitioner or specialist (30%). In most cases information was sought from multiple sources.

Users experienced several side effects. Palpitations were reported most frequently (47%). Irritability was experienced in 31%, agitation in 28% and headache in 25% of users. Amongst the unlisted side effects ('Other'), insomnia was mentioned most often (14%).

No significant association was found between prescription nootropic use and age ($p=0.136$), gender ($p=1$) or seniority ($p=0.178$). The use of nootropics did not predispose to the use of prescription smart drugs ($p=0.237$). There was no association between smoking cigarettes or e-cigarettes and the use of nootropics ($p=0.753$) or smart drugs ($p=0.702$). There was no association between smart drug use and having friends that consumed smart drugs ($p=0.422$). Taking smart drugs was also not associated with using 'downers' ($p=0.089$). Almost all participants consumed some form of caffeinated drink (99%) and so no comparison with the nootropic and smart drug data set was possible.

When asked whether respondents knew of colleagues taking medication for neurocognitive enhancement, 76% responded they did. An association existed with age, such that a lower proportion of individuals over 40 years of age knew of someone taking medication for the previously mentioned purpose ($p=0.035$).

Of the respondents who did not use nootropics, one third ($n=32$) had considered taking medication for neurocognitive enhancement. The most common reason for not taking prescription nootropics was the fear of side effects (43%), as well as not knowing enough about the medications (39%), being wary of addiction (36%) and having no need for such (33%). There was a significant association between age and being a non-user, such that younger non-users were more likely to have considered taking prescription nootropics ($p=0.008$). In addition, there was an association between seniority and non-use of prescription nootropics. Consultants had the lowest proportion of non-using participants who had considered taking prescription nootropics ($p=0.001$).

An ideal neurocognitive enhancer is defined as one devoid of side effects, including addiction.[3] When asked whether the respondent would consider taking an ideal neurocognitive enhancer, 81% of respondents indicated they would take such a medication. No significant association was found between ideal nootropic use and age ($p=0.858$), gender ($p=0.511$) or seniority ($p=0.174$).

In terms of substances used to relax, 55% of respondents had used a 'downer' (figure 4). Where the question allowed for open response ('Other'), two respondents quoted β-blocker use, amitriptyline and one quoted use of sertraline. No significant associations were found between 'downer' use and age ($p=0.629$), gender ($p=0.491$) or seniority ($p=0.554$).

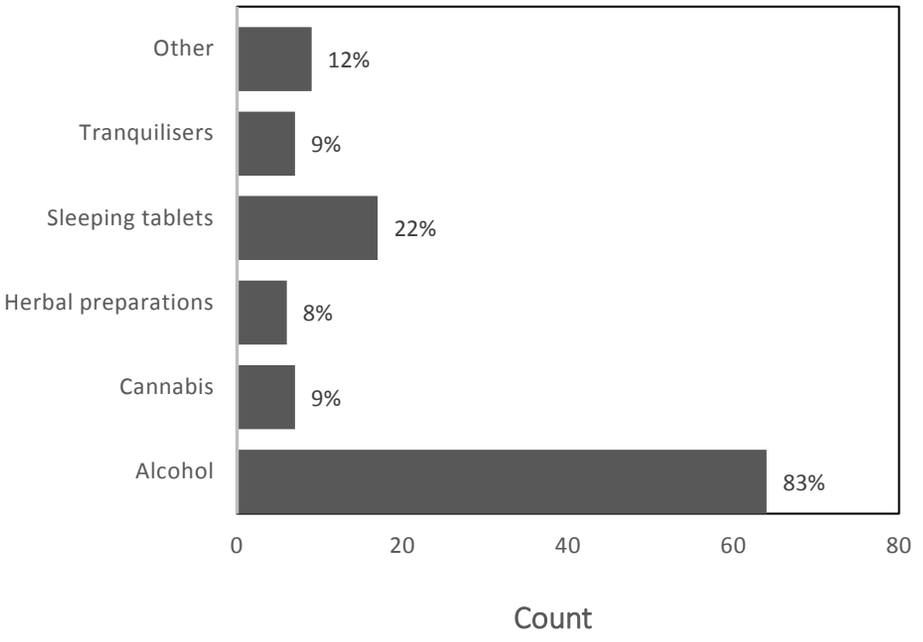

Figure 4 Downers

Discussion

The prevalence of neurocognitive enhancement within the Department of Anaesthesiology at the University of the Witwatersrand is similar to that seen in the United States of America (25% compared to 8.1 to 27.6%).[6] When compared to European and Australian data, it is much more prevalent in this Department, with European statistics at 0.78% to 6.2% and Australian figures of 1.4% to 4.4%.[1, 8, 9] This could be explained by the South African context of a developing nation where limited resources, both financial and human, generate an unprecedented level of stress.[15] It has been established that this can lead to burnout in this setting.[15, 16]

The nootropic agents that are being used are comparable with those used elsewhere. Coffee is reported with a high prevalence, although this seems to not be motivated by neurocognitive enhancement in this setting. Interestingly, this remains a motivation for the use of other caffeinated beverages, an idea which may be influenced by media and advertising. Non-caffeinated energy drink use was mostly motivated by enhanced sports performance, despite research showing increased neurocognitive enhancement when compared to caffeinated drinks.[7] An age distinction seems to exist. Those over 40 years of age all consumed coffee, but tended not to consume non-caffeinated energy drinks.

A marked difference exists in the prescription nootropics or smart drugs being used and this is in keeping with the availability of certain agents in South Africa. Amphetamines and dextroamphetamines (Adderall) are not readily available in South Africa. This study shows that methylphenidate is mostly used, followed by modafinil.

More respondents took nootropics rather than smart drugs, which is to be expected.[3, 7] These nootropics are generally used to enhance neurocognition but are perceived to cause less side effects and have less addiction potential, thus making their use more acceptable.[3] Access is also made easier by nootropics being available over-the-counter. Many respondents expressed an inherent fear of the perceived addiction potential of smart drugs. According to Smith et al [17] and Swanson et al,[18] one in twenty users will develop addiction. Dependence has been demonstrated by cravings, anxiety and depression following abrupt cessation of intake.[1]

The motivation of those that consumed smart drugs were similar in nature and proportion to those reported in international literature.[1, 3, 5, 7, 8, 10, 12] Smart drugs were used to improve concentration in 69% of respondents, compared to 65.2% quoted in the literature.[6] Internationally, 59.8% used smart drugs for studying.[6] This study found that 83% consumed smart drugs during periods of examination.[6, 11]

Smart drugs have shown consistent positive effects in increasing processing accuracy, as well as enhancing cognitive perseveration and flexibility.[11] Amphetamines appear to be superior to methylphenidate in this regard.[7] Methylphenidate has been shown to improve memory.[11] It may, however, exhibit an inverted U-shape function, whereby too high or too low a dose may impair performance, requiring a moderate dose to show neurocognitive enhancement.[19] Amphetamines were shown to improve consolidation of newly acquired information and declarative learning.[7] Where some stimulants have a tendency to increase wakefulness or mood, it is noted that although not direct, cognitive enhancement may be a secondary effect of such.[17] This is shown by the enhancement lasting well beyond the time of drug action.[17] Modafinil may improve attention in well-rested subjects, but for those with sleep deprivation, might maintain wakefulness whilst improving memory and executive functions to a significantly higher degree.[19] Despite these findings, some studies report null results, making an absolute statement on whether smart drugs increase cognition, impossible.[11, 17, 19] There are, however, no studies that report overall performance impairment.[11, 17]

Routes of obtaining smart drugs are similar to those seen in international trends with the majority making use of loose tablets.[10] Studies have identified that the most common routes of obtaining smart drugs is by receiving limited doses from friends or family who are prescribed the substances as treatment for medical conditions. Other routes include falsified prescriptions, prescriptions issued by medical professionals, internet sites and drug dealers.[1, 4, 8, 9, 17] In the United States of America, 30% of prescriptions were for non-medical use in 2008.[18] This correlates with the result of approximately 30% obtained in this study, where prescriptions were either self-written, administered by friends or colleagues or from general practitioners or specialists.

Side effects associated with the consumption of smart drugs and their frequency are in keeping with international findings that slightly under a third of users report experiencing side effects.[1, 10]

This study showed that the decision to take smart drugs was generally made following prior investigation of drugs. Information is mostly gathered from the internet but also obtained from several other sources, including consultation with colleagues, family, friends and medical professionals. Steward et al [12] state that students in particular, were noted in various studies to have conducted their own research prior to using smart drugs and had made use of their lay pharmacology to substantiate utilisation. This may indicate that smart drug use is not the reckless practice described by many critics. Instead, it is a meticulous weighing up of

risks versus benefits in the context of pharmaceuticalisation where human capacities, conditions and capabilities are open to transformation by pharmacological intervention.[4, 12]

That over 80% of respondents who knew of someone taking smart drugs, were under the age of 40 years, suggests that neurocognitive enhancement is a fairly new trend. The younger cohort was also more open to the idea of experimentation. Knowledge regarding nootropics and neurocognitive enhancement, however, was high among the entire cohort. This is likely due to sampling a highly academic group where pharmacology is the mainstay of the profession.

Where 'downers' are concerned, there seems to be a preponderance towards alcohol consumption in this study. Alcohol consumption carries less stigma compared to other 'downers'.[10] Sleeping tablet use is also common and is expected in a profession where the customisation of sleep can be justified by shift work. Cannabis use was only noted in 9% of users, but could in truth be much more common.[10] The stigma associated with cannabis would skew this result.[10] Although not addressed in this study, some studies have started looking at the use of alcohol and cannabis as a form of neuroenhancement.[10] This is based on a concept of sedative substances allowing for stress control and thus improving neurocognition.[10]

This study did not aim to examine behaviour patterns around the use of illicit substances. However, the study's cohort has significant understanding and access to prescription tranquilisers, and so could be more prone to the use of prescription 'downers'. This may warrant further investigation.

The quest for improved neurocognition is ongoing. In order to accurately quantify brain doping, standardised surveys would need to be conducted regularly to establish local and global trends. A need for objective measures also exists. Brugard et al [20] showed how this could be achieved. Their study tested college wastewater for amphetamine and ritalinic acid levels during low-stress weeks, compared to examination time.[20] Wilms et al [4] have suggested body fluid testing. Similar studies would need to be conducted in our setting to accurately quantify the practice of smart drug use.

Further studies are also needed to elucidate the impact of smart drugs on cognitive performance, based on specific agents with different mechanisms of action. The effect of smart drugs on consumers with and without ADHD or traits thereof, as well as pharmacological mechanisms of these effects, remains to be evaluated. Potential genetic and neurodevelopmental variation, such as catechol-O-methyltransferase genotype, may underlie the cognitive and behavioural effects of smart drugs .[11] It is also difficult to quantify a baseline of neurocognition with the effect of cognitive enhancement achieved by exercise, nutrition, healthy sleep patterns and stress management.[17]

The question that arises is whether smart drug use is more prevalent in other sectors of society or whether it is limited to the medical fraternity. Prevalence would need to be established in the corporate and management sectors, as well as amongst university and school-going students.

The ethical debate regarding brain doping will likely always be present. This study shows that smart drug use is fairly common in this department and largely used for neuroenhancement specifically to support academic endeavour. A realistic approach should be adopted, together with an open discussion on advantages, disadvantages and the acceptability of such. Non-medical use of pharmaceutical agents is becoming more prevalent and presents a far greater risk to society than controlled, scheduled and medically motivated

distribution of medicines. Looking at 'doping' in sport, the initial motivation behind banning such behaviour, was to safeguard the athlete, which would be the rationale behind regulating smart drugs.[21] It may be that different substances require different levels of regulation, as well as for different uses of the same substance.[21] In the United Kingdom, the Academy of Medical Sciences has recommended the establishment of regulating authorities for cognitive enhancers.[19] Although such structures do not exist in South Africa at present, the implementation of protocols and regulations should be considered.

Smart drug misuse may have serious side effects. The need for policy delineating smart drug use may be required in the future. This should be driven by interdisciplinary research and it remains to be established whether policy should be restrictive or liberal. The ethical and legal implications of prescription drugs must also be evaluated. Maier et al [22] showed that 48% of Swiss university students felt that access to pharmacological cognitive enhancers increased the pressure to engage in their use. One should, however, remember that subjective effects ultimately motivate users to take smart drugs, rather than objective results of neuropsychological assessments.[19] It remains to be determined whether utilitarian ethics justifies promoting research into medications intended to enhance the human condition, rather than medications for conventional medical therapy.[19, 23]

The basis of 'brain doping', however, remains the positive enhancements and 'motivators' which lead consumers to seek smart drugs. Neglecting to address these issues, will allow the practice to continue unchecked. Neurocognitive enhancement should be understood against the backdrop of increasing societal pressure to achieve, live and work, often disregarding biological rhythms and therefore underlies the concept of 'wellness'.[19]

Limitations

Generalisability of results may not be possible as the sample was limited to a single department. The study is also contextual. The subject matter is of a sensitive nature and thus results rely on the transparency of the respondents. The fear of negative repercussions in a hierarchical organisation may limit honesty among participants, despite the anonymity offered by the study's design. Studies that have employed randomised response techniques which offer a high degree of anonymity and privacy, have suggested a four times higher prevalence rate when compared to paper-and-pencil questionnaires.[7]

Where respondents may have been reluctant to participate, a risk of recruitment bias may have led to a skewing of results. Data collection was carried out during the COVID-19 pandemic. This period of unprecedented workplace stress may have adversely influenced results, based on respondents being ill or quarantined.

Studies regarding smart drugs vary greatly in terms of design, population, and questionnaire content and results must therefore be compared cautiously.

Conclusion

Neurocognitive enhancement is a practice achieved by the use of smart drugs, nootropics and stimulants. This study demonstrated that there is a notable prevalence of smart drug use in the Department of Anaesthesiology at the University of the Witswatersrand. It has also highlighted that a significant number of respondents use smart drugs as a coping mechanism to address the academic demands associated with specialising in anaesthesiology.

Furthermore, smart drug use in this department follows similar trends to those found internationally.

It appears that trainees may be particularly at risk of engaging in ‘brain doping’. A paucity of literature regarding long term risks, makes this an area that requires further research in terms of establishing local prevalence. The need to modify current systems to alleviate the burden of academic and work load pressures, with improved quality of care for both patients and doctors, exists. The drafting of internal policies in terms of cognitive enhancement may mitigate the risk in this group. Ultimately, neuroenhancement is so much more than the pursuit of academic excellence, but rather the enhancement of modern work-life balance and thus cannot be ignored.

References

1. Majori S, Gazzani D, Pilati S et al. Brain doping: stimulants use and misuse among a sample of Italian college students. J Prev Med Hyg. 2017;58(2):E130-E140. https://www.ncbi.nlm.nih.gov/pubmed/28900353.
2. Franke AG, Christmann M, Bonertz C, Fellgiebel A, Huss M, Lieb K. Use of coffee, caffeinated drinks and caffeine tablets for cognitive enhancement in pupils and students in Germany. Pharmacopsychiatry. 2011;44(7):331-338. DOI: 10.1055/s-0031-1286347.
3. Pighi M, Pontoni G, Sinisi A et al. Use and Propensity to Use Substances as Cognitive Enhancers in Italian Medical Students. Brain Sci. 2018;8(11). DOI: 10.3390/brainsci8110197.
4. Wilms W, Woźniak-Karczewska M, Corvini PF, Chrzanowski Ł. Nootropic drugs: Methylphenidate, modafinil and piracetam - Population use trends, occurrence in the environment, ecotoxicity and removal methods - A review. Chemosphere. 2019;233:771-785. DOI: 10.1016/j.chemosphere.2019.06.016.
5. Finger G, Silva ER, Falavigna A. Use of methylphenidate among medical students: a systematic review. Rev Assoc Med Bras (1992). 2013;59(3):285-289. DOI: 10.1016/j.ramb.2012.10.007.
6. Teter CJ, McCabe SE, LaGrange K, Cranford JA, Boyd CJ. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. Pharmacotherapy. 2006;26(10):1501-1510. DOI: 10.1592/phco.26.10.1501.
7. Franke AG, Bagusat C, Rust S, Engel A, Lieb K. Substances used and prevalence rates of pharmacological cognitive enhancement among healthy subjects. Eur Arch Psychiatry Clin Neurosci. 2014;264 Suppl 1:S83-90. DOI: 10.1007/s00406-014-0537-1.
8. Liakoni E, Schaub MP, Maier LJ, Glauser GV, Liechti ME. The Use of Prescription Drugs, Recreational Drugs, and "Soft Enhancers" for Cognitive Enhancement among Swiss Secondary School Students. PLoS One. 2015;10(10):e0141289. DOI: 10.1371/journal.pone.0141289.
9. Jensen C, Forlini C, Partridge B, Hall W. Australian University Students' Coping Strategies and Use of Pharmaceutical Stimulants as Cognitive Enhancers. Front Psychol. 2016;7:277. DOI: 10.3389/fpsyg.2016.00277.
10. Maier LJ, Liecht, M. E., Herzig, F., Schaub M. P. To Dope or Not to Dope: Neuroenhancement with Prescription Drugs and Drugs of Abuse among Swiss University Students. PLoS One. 2013;8(11):e77967. DOI: 10.1371/journal.pone.0077967.
11. Marraccini ME, Weyandt LL, Rossi JS, Gudmundsdottir BG. Neurocognitive enhancement or impairment? A systematic meta-analysis of prescription stimulant effects on processing speed, decision-making, planning, and cognitive perseveration. Exp Clin Psychopharmacol. 2016;24(4):269-284. DOI: 10.1037/pha0000079.
12. Steward A, Pickersgill M. Developing expertise, customising sleep, enhancing study practices: exploring the legitimisation of modafinil use within the accounts of UK undergraduate students. Drugs (Abingdon England). 2019;26(4):347-355. DOI: 10.1080/09687637.2018.1555231.
13. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194. DOI: 10.1001/jama.2013.281053.
14. Africa DoHRoS. South African Good Clinical Practice: Clinical Trial Guidelines. In: Health Do, editor. 3rd ed. Pretoria, South Africa 2019
15. Groenewald MB vNJ, Parker R. Are Groote Schuur Hospital anaesthesiologists burnt

out? A cross-sectional study of prevalence and risk. Southern African Journal of Aneasthesia and Analgesia. 2020;26(3):151-161. DOI: 10.36303/SAJAA.2020.26.3.2341.
16. van der Walt NS, Scribante J, Perrie, H. Burnout among anaesthetists in South Africa. Southern African Journal of Aneasthesia and Analgesia. 2015;21(6):169-172. DOI: 10.1080/22201181.2015.1102798.
17. Smith ME, Farah MJ. Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. Psychological bulletin. 2011;137(5):717-741. DOI: 10.1037/a0023825.
18. Swanson JM, Wigal TL, Volkow ND. Contrast of medical and nonmedical use of stimulant drugs, basis for the distinction, and risk of addiction: comment on Smith and Farah (2011). Psychological bulletin. 2011;137(5):742-748. DOI: 10.1037/a0024898.
19. Repantis D, Laisney O, Heuser I. Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: a systematic review. Pharmacol Res. 2010;61(6):473-481. DOI: 10.1016/j.phrs.2010.02.009.
20. Burgard DA, Fuller R, Becker B, Ferrell R, Dinglasan-Panlilio MJ. Potential trends in Attention Deficit Hyperactivity Disorder (ADHD) drug use on a college campus: Wastewater analysis of amphetamine and ritalinic acid. Science of The Total Environment. 2013;450-451:242-249. https://doi.org/10.1016/j.scitotenv.2013.02.020.
21. Lucke JC, Bell SK, Partridge BJ, Hall WD. Academic doping or Viagra for the brain? The history of recreational drug use and pharmacological enhancement can provide insight into these uses of neuropharmaceuticals. EMBO Rep. 2011;12(3):197-201. DOI: 10.1038/embor.2011.15.
22. Maier LJ, Liakoni E, Schildmann J, Schaub MP, Liechti ME. Swiss University Students' Attitudes toward Pharmacological Cognitive Enhancement. PLoS One. 2015;10(12):e0144402. DOI: 10.1371/journal.pone.0144402.
23. Beyer C, Staunton C, Moodley K. The implications of methylphenidate use by healthy medical students and doctors in South Africa. BMC Med Ethics. 2014;15:20. DOI: 10.1186/1472-6939-15-20.

APPENDICES

Appendix 1: Proposal

Appendix 2: Human Research Ethics Committee clearance certificate

Appendix 3: Plagiarism/Turnitin report cover page

Appendix 4: Journal guidelines to authors (SAMJ)

Appendix 5: Permission letter by the Anaesthesiology Head of Department

Appendix 6: Checklist (PRISMA/STROBE/CONSORT)

Appendix 1

Smart drug use in the Department of Anaesthesiology at the University of the Witwatersrand

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Department of Anaesthesiology

Supervisor 2: *Dr Razeena Lockhat*

Department of Anaesthesiology

1. Introduction

Increasing academic and work demands provide a conducive environment for the use of stimulants and prescription drugs for cognitive enhancement. This trend has been noted in students at scholastic, undergraduate and postgraduate level. It has also been described in the work population (1).

Cognitive enhancement entails the use of psychoactive drugs by healthy individuals. This is also known as pharmacological neuroenhancement, cosmetic neurology, academic performance enhancement, as well as academic, intellectual or brain doping (2). Cognitive functions that can be enhanced include attention, vigilance, concentration, memory and mood (2, 3).

The phenomenon initially surfaced in the United States of America, but has now been reported in various European countries, as well as Australia, New Zealand, and certain South American nations (2, 4-9). Prevalence rates in the United States of America range from 8.1% to 27.6%, with a preponderance towards amphetamine-dextroamphetamine (Adderall) use (5). Of these, lifetime use and past-year prevalence were found to be 8.3% and 5.9% respectively. In Europe, prevalence tends to be lower with rates of 0.78% in Germany to 6.2% in Switzerland, with methylphenidate as the common drug of choice (2, 7, 10). Australian statistics show a prevalence between 1.4% and 4.4% (9). New Zealand has a prevalence of 6.6% (9).

Substances commonly associated with cognitive enhancement include over-the-counter stimulants (coffee, caffeinated/energy drinks, caffeine tablets, Ginkgo biloba), nootropics, smart drugs (methylphenidate, amphetamines, modafinil, acetylcholinesterase inhibitors) and illicit drugs (6).

Nootropics were first described in 1972 based on the model drug, piracetam (8). These were initially defined as non-toxic and safe psychotropic drugs activating brain mechanisms to compensate for central nervous system deficits, without induction of reticular, subcortical or limbic responses. They also facilitate learning and improve memory (8). In recent times, “smart drugs” has become the descriptor for nootropics that are prescribed for certain neurological disorders, but used by healthy individuals in the pursuit of cognitive enhancement (8). This raises legal and ethical concerns as to how the substances are obtained.

Studies have identified that the most common routes of obtaining smart drugs is by receiving limited doses from friends or family who are prescribed the substances as treatment for medical conditions, falsified prescriptions, prescriptions issued by medical professionals, internet sites and drug dealers (2, 7-9, 11). Thirty percent of stimulant prescriptions in the United States in 2008, were diverted to non-medical use (12). This subversion of medical practice has caused stigmatisation of pharmaceutical cognitive enhancement. The motivators, however, continue to sway users to seek out substances (12).

Motivators include improving concentration (65.2%), assisted studying (59.8%), increasing alertness (47.5%), "getting high" (31.0%) and experimentation (29.9%) (5, 13). Other reasons driving smart drug use are weight loss, improving performance in the face of sleep deprivation and customising sleep-wake cycles (14). Use is usually increased in periods of heightened stress, such as examinations. These motivators underlie an adaptive response to an ever increasing competitiveness in the academic and sociocultural spheres, demanding increased productivity. This is coupled with anecdotal sources of stress such as self and familial expectations, time constraints, peer pressure, financial and career considerations (2, 7, 9).

Several factors are associated with smart drug use. These are intrapersonal risk factors such as Caucasian ethnicity, poor academic performance, previous use (e.g. at school or undergraduate level) and low self-esteem (2). Interpersonal factors include off-campus residence, participation in various sports, use as socialising agents and media exposure (2, 5).

Users justify consumption based on the substances' prescription statuses implying increased safety, as medical drugs are accompanied by dosages and are thus perceived as being safer than street drugs. Steward et al (14) state that students in particular, were noted in various studies to have conducted their own research prior to using smart drugs and had made use of their lay pharmacology to substantiate utilisation. This may indicate that smart drug use is not the reckless practice described by many critics. Instead, it is a meticulous weighing up of risks versus benefits in the context of pharmaceuticalisation where human capacities, conditions and capabilities are open to transformation by pharmacological intervention (8, 14).

The question arises as to whether there is any established evidence of smart drug use objectively enhancing cognition. A recent meta-analysis by Marraccini et al (13) looked at the parameters of planning, processing speed, cognitive perseveration and decision-making

among healthy subjects taking smart drugs. Processing speed is the amount of time taken to make an accurate judgement of stimulus (13). Planning and decision-making require looking ahead, formulating alternatives and making objective assessments based on conceptual frameworks (13). Impulse control, sustained attention and memory underlie the latter processes (13). Attention may be defined as appropriate allocation of processing resources to relevant stimuli. Motivation alludes to initiation, direction, intensity and persistence of behaviour. Executive functions are those where the ability to practise flexible, task-appropriate responses are tested by disregarding irrelevant, competing inputs or more habitual, but inappropriate response patterns (15). Cognitive perseveration measures the individual's ability to shift thinking when the rules of a task change (13).

Smart drugs had consistent positive effects in increasing processing accuracy, as well as enhancing cognitive perseveration and flexibility (13). Amphetamines appear to be superior to methylphenidate in this regard (6). Methylphenidate has been shown to improve memory. It may, however, exhibit an inverted U-shape function, whereby too high or too low a dose may impair performance, requiring a moderate dose to show neurocognitive enhancement (15). Amphetamines were shown to improve consolidation of newly acquired information and declarative learning (6). Where some stimulants have a tendency to increase wakefulness or mood, it is noted that although not direct, cognitive enhancement may be a secondary effect of such (11). This is shown by the enhancement lasting well beyond the time of drug action (11). Modafinil may improve attention in well-rested subjects, but for those with sleep deprivation, might maintain wakefulness whilst improving memory and executive functions to a significantly higher degree (15). Despite these findings, some studies report null results, making an absolute statement on whether smart drugs increase cognition, impossible. There are, however, no studies that report overall performance impairment (11, 13). It has been suggested that outcomes may be based on individual baseline performance, namely the intelligence quotient of the individual (15).

Measuring the extent of cognitive enhancement is difficult, and results based on task tests vary widely. This may be due to individual characteristics that modulate smart drug effect. Personality, ability level and catechol-O-methyltransferase (COMT) genotype are some of the characteristics that have been identified (11). Together with this, weight-based dosing must not be overlooked. It is also difficult to quantify the effect of background cognitive enhancement achieved by exercise, nutrition, healthy sleep patterns and stress management (11). Furthermore, perceived cognitive enhancement may be accounted for by placebo effects

or alter perceptions of the amount or quality of work produced, rather than produce an objective alteration in the work (11).

Amphetamines and methylphenidate work by increasing catecholamines in the prefrontal cortex, as well as the cortical and subcortical regions projecting to it (8). This has shown benefit in the treatment of attention deficit hyperactivity disorder. Amphetamines increase the rate of release of dopamine from presynaptic neurones and prevent reuptake, allowing for increased levels to accumulate in the synaptic cleft. Methylphenidate works by primarily inhibiting reuptake of dopamine. This results in hyperstimulation of the sympathetic nervous system which plays a vital role in enhanced cognition, increasing focus and attention. Furthermore, activation of the ventral striatum, nucleus accumbens and other reward centres in the brain, account for pleasurable feelings, and thus may lead to addiction (5, 8, 11).

Modafinil, approved for the management of narcolepsy, causes dopamine and noradrenaline release from dopaminergic and gamma-aminobutyric pathways in the prefrontal cortex (8). It may also play a role in glutamate, histamine and orexin/hypocretin systems (15). Adrafinil (2-[(diphenylmethyl)sulfinyl]-N-hydroxyacetamide) is the prodrug of modafinil and can thus be metabolised in the liver to such (8). Piracetam, initially used in Alzheimer's and dementia patients, works on cholinergic, dopaminergic and noradrenergic neurotransmitter systems, simultaneously protecting neurons from toxins and aiding in the re-establishment of damaged neurotransmission (8). Acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine, prevent enzymatic degradation of acetylcholine in the synaptic cleft, allowing levels to accumulate. Although beneficial in the treatment of dementia, there has been no proven cognitive enhancement among healthy individuals, although donepezil has been shown to improve retention of training on complex aviation tasks and verbal memory for semantically processed words (15). In individuals with sleep deprivation, donepezil was shown to reduce memory and attention deficits (6, 15). Memantine works as an N-methyl-D-aspartic acid receptor antagonist (15).

For more common stimulants, caffeine has been proven to increase vigilance and wakefulness, but not directly enhance cognition (6). Some studies have, however demonstrated that caffeine may be as effective as methylphenidate and amphetamines in enhancing vigilance and psychomotor function (3, 6). Interestingly, energy drinks, with or without caffeine content, have been shown to increase vigilance and wakefulness too, but to a

greater degree when compared to coffee (6). Ginkgo biloba has shown no effect on cognition, vigilance, attention or reaction time (6).

Smart drug use is accompanied by a host of multisystemic side effects. Tachycardia, arrhythmias and angina are among the cardiovascular side effects. Agitation, aggressiveness, confusion, tremors, hyperactivity, headache, mydriasis and mood swings may manifest neurologically. Gastrointestinal effects include abdominal pain, anorexia and nausea. Toxic side effects include hyperthermia, delirium, euphoria, hallucinations and seizures (2). One study reported that 29.4% of users had experienced one or more serious side effects (2). The route of administration (oral, intranasal, smoking or intravenous) may rapidly increase serum concentration and lead to increased side effects (5). This may impact on long term health, as well as present an economic and social burden in terms of the increase in resources needed to manage these patients. Importantly, the potential for dependence and addiction remain inherent (2).

Because of stimulation of reward centres in the brain and common personality traits among users, addiction is a concern. According to Smith et al (11) and Swanson et al (12), one in twenty users will develop addiction. Dependence has been demonstrated by cravings, anxiety and depression following abrupt cessation of intake (2). Methylphenidate, dextroamphetamine and mixed amphetamine salts are as such scheduled as Schedule II controlled substances in the United States (12). Of these, only methylphenidate is available in South Africa and is a schedule 6 drug (16).

Studies have shown that in the United States, amphetamine-dextroamphetamine is at present more popular than methylphenidate (5). Hypotheses as to why this is the case are based on ease of accessibility, increased efficacy compared to methylphenidate and less emotional imbalance (5). Adderall XR, an extended-release amphetamine-dextroamphetamine formulation, has a duration of action between 10 and 12 hours compared to methylphenidate which lasts six hours, thus exhibiting fewer emotional fluctuations compared to methylphenidate (5). Amphetamine-dextroamphetamine also causes a higher accumulation of dopamine presynaptically and increased levels of norepinephrine which are generally perceived as resulting in better cognitive enhancement (5).

Recent research has delved into the use of sedative substances including alcohol and cannabis, in achieving cognitive enhancement. The role of sedatives in this capacity is not to directly enhance learning processes, but rather to improve performance by a ‘well rested’

brain. Restorative sleep has been shown to increase vigilance and concentration upon awakening (10).

Non-pharmaceutical high tech cognitive enhancement methods have also been described (11). Transcranial magnetic stimulation consists of inducing weak currents in specific brain areas by magnetic fields generated outside the cranium. Initially targeted at treating conditions such as depression and attention deficit hyperactivity disorder, it has been found to increase cognition in healthy individuals (11). There has also been renewed interest in transcranial direct current stimulation. Evidence exists for improved learning and enhanced planning with transcranial direct current stimulation (11).

The policy on whether smart drug use should be liberal or restrictive, needs to address the underlying motivators. One method of mitigating abuse in academic settings, may be spreading out assessments in order to avoid periods of intense stress. Such strategies would address not only smart drug use, but individual mental health and wellness too (14).

In recent times, pharmaceuticalisation has allowed the customisation of appetite, mood, sleep and sex (11). It is therefore not surprising that cognitive enhancement has become the next frontier. Corneliu Giurgea, who is credited with coining the term nootropic, stated, “Man is not going to wait passively for millions of years before evolution offers him a better brain.” (11)

In the medical academic setting, there is an underlying culture of smart drug use for cognitive enhancement due to the demands of training. This, however, has not been explored in our setting. Furthermore there is a paucity of studies reporting this at all in South Africa. The aim of this research project was to probe the subject of cognitive enhancement within the microsphere of the Department of Anaesthesiology at the University of the Witwatersrand.

2. Problem statement

Cognitive enhancement by smart drug usage is growing in popularity and affecting upcoming generations. To many it promises to be the panacea sought to resolve the overwhelming stress suffered by academics and those in demanding professions. Anaesthesiology demands rigorous academia combined with stringent working conditions. The question arises as to whether smart drug consumption is used as a coping strategy. This research project will probe

the subject of cognitive enhancement within the microsphere of the Department of Anaesthesiology at the University of the Witwatersrand.

3. Aims

The aim of this study is to describe the use of nootropics and smart drugs in the context of cognitive enhancement by those working in the Department of Anaesthesiology at the University of the Witwatersrand.

4. Objectives

Primary objective

- To describe the prevalence of smart drug use amongst medical officers, registrars and consultants in the Department of Anaesthesiology.

Secondary objectives

- To describe gender, age differences and years of experience in the use of smart drugs.
- To describe which smart drugs are commonly used.
- To describe the frequency of use.
- To identify possible underlying motivators.
- To describe routes of obtaining the various substances.
- To identify and describe preferences between prescription versus over-the-counter preparations.
- To identify previous use.
- To describe the effects experienced by users.
- To describe nervous system depressants used to counter the effects of stimulants.

5. Research assumptions

The following definitions will be used in the study.

Anaesthetist: is any qualified doctor working in the Department of Anaesthesiology, including medical officers, registrars and consultants.

Intern: is a doctor who completed a university degree, but is currently undergoing practical training prior to registration with the Health Professionals Council of South Africa as an independent practitioner.

Medical officer: is a qualified doctor practising in the Department of Anaesthesiology under specialist supervision. This will include those performing community service. Medical officers with more than ten years of experience are career medical officers and are regarded as consultants.

Registrar: is a qualified doctor who is registered with the Health Professions Council of South Africa as a trainee anaesthetist.

Consultant: is a specialist anaesthesiologist or career medical officer.

Stimulant: any substance that results in sympathetic nervous system output.

Depressant: any substance that increases parasympathetic nervous system output or dampens the sympathetic nervous system response.

Nootropic: any substance used to facilitate learning and improve memory (8). In this study, nootropics will be limited to over-the-counter drugs used in this capacity.

Smart drugs: prescription drugs used for cognitive enhancement and found in the South African Medicines Formulary (16).

6. Demarcation of study field

The study will be conducted in the Department of Anaesthesiology, affiliated to the Faculty of Health Sciences of the University of the Witwatersrand. The staff complement of the department is 74 consultants, 112 registrars and 22 medical officers. The following hospitals constitute the core academic and training platform.

- Charlotte Maxeke Johannesburg Academic Hospital a 1200-bed central hospital.
- Chris Hani Baragwanath Academic Hospital a 3200-bed central hospital.
- Helen Joseph Hospital a 500-bed regional hospital.
- Rahima Moosa Mother and Child Hospital a 338-bed regional hospital.
- Wits Donald Gordon Medical Centre a public-private hospital with 190 beds.
- Thelle Mogoerane (Natalspruit) Hospital an 820-bed regional hospital.

7. Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand. Permission will also be sought from the Head of Department of Anaesthesiology.

Participants will be given a letter of introduction attached to the questionnaire. Participation will be completely voluntary and anonymous. Consent is implied by completion of the questionnaire. Responses will not be able to be traced back to any individual.

In terms of distributive justice, the study aims to identify any negative motivators for stimulant use, such as academic pressure, work load, etc. and address this in a holistic manner within the Department to ensure the continued wellness of the specialist body. This may entail a workshop teaching coping strategies.

Data will be stored securely for a period of six years after completion of the study. Paper questionnaires will be stored in a file in a locked cupboard. Electronic data will be password protected.

The study will be conducted according to the principles of the Declaration of Helsinki (17) and the South African Guidelines for Good Clinical Practice (18).

8. Data collection

8.1 Research design

A prospective, descriptive, contextual, observational, qualitative research design will be followed in this study.

The study is an observational study that analyses data from a representative subset of the population at a specific point in time.

It is qualitative and descriptive as it describes the pattern of smart drug use in relation to denoted variables and gathers non-numerical data.

8.2 Study population

The study population will consist of medical officers, registrars and consultants in the Department of Anaesthesiology at the University of the Witwatersrand.

8.3 Study sample

Sample method

In this study, a convenience sampling method will be used. This is a type of non-probability sampling where the sample is taken from that part of the population that is close at hand.

Sample size

The entire body of 22 medical officers, 112 registrars and 74 consultants will be sampled. Sample size is thus 208. This sample size has been discussed in consultation with a biostatistician. A response rate of 65% (n=136) is considered acceptable. The acceptable margin of error will be 5%, the confidence interval 95% and the response distribution is 50%.

Inclusion and exclusion criteria

The inclusion criteria for this study are:

- Medical officers currently employed in the Department of Anaesthesiology at the University of the Witwatersrand hospitals.
- Registrars registered with the University of the Witwatersrand and working in the Department at the time of data collection.
- Consultants currently working in the Department of Anaesthesiology at the University of the Witwatersrand.

The exclusion criteria for this study:

- Interns are to be excluded.

8.4 Collection of data

The study will generate its own questionnaire based on the current literature. This will be reviewed by three external consultants in the Department of Anaesthesiology, as well as one external public health specialist. Collection of data will be by means of a voluntary and anonymous multiple choice, self-administered, paper-based questionnaire (appendix A). The questionnaire will be handed out to consultants, registrars, medical officers and community service medical officers working in the Department, until the required response rate is achieved. It is to be folded in half upon completion and posted into the sealed boxes placed in the various departmental tearooms.

9. Data analysis

Data analysis will be performed with the assistance of a biostatistician using Stata/SE 13.1 statistical software (Copyright 1985–2013 Stata Corp LP Statistics/Data Analysis Stata Corp 4905 Lakeway Drive Special Edition College Station, Texas 77845 USA 800–STATA–PC http://www.stata.com, stata@stata.com).

Normally distributed data will be presented as mean and standard deviation, whereas skewed data will be presented as median and interquartile range for skewed distribution. Categories will be analysed using Chi squared and the Fisher's exact test. Statistical significance is denoted by a *p* value of less than 0.05.

10. Significance of the study

The study is significant as it would be the first survey conducted in the Department of Anaesthesiology at the University of the Witwatersrand, regarding smart drug use. It plays an integral role in indirectly establishing wellness. It may aid in the modification of current systems to alleviate the burden of academic and work load pressures, with improved quality of care for both patients and doctors. Results should not be used punitively, but rather to protect individuals from a potentially addictive practice. Workshops designed to educate anaesthetists about the dangers of smart drug use could be developed and presented. It may even allow the drafting of internal policies in terms of cognitive enhancement.

11. Validity and reliability of the study

Validity and reliability ensure an appropriate research design. Content validity of the instrument is established by an extensive literature review. Content and face validity are ensured by review of the instrument by senior and external parties, as mentioned above. One researcher is to collect all data. The researcher will be present for questions. Data will then be analysed in conjunction with a biostatistician. Reliability of the study depends on the truthfulness of the respondents, which is noted below as one of the limitations of the study.

12. Potential limitations of the study

Contextual design and convenience sampling may preclude generalisability of the study. The study is also limited by the sensitivity of the subject matter and the truthfulness of the respondents.

13. Project outline

Activity	Sep 2019	Oct 2019	Nov 2019	Dec 2019	Jan 2020	Feb 2020	Mar 2020	Apr 2020	May 2020	Jun 2020
Proposal preparation										
Literature review										
Proposal submission										
Ethics approval										
Postgraduate approval										
Data collection										
Data analysis										
Draft article										
Submission										

14. Financial plan

Costs incurred amount to printing costs. These are to be borne in part by the primary author and the department.

Item	Price per page	Number of pages	Copies	Total
Proposal	1.50	15	10	R 225
Ethics	1.50	10	25	R 375
Post graduate form	1.50	2	6	R 18
Complete report	1.50	30	4	R 180
Grand total				**R 798**

15. References

1. Pighi M, Pontoni G, Sinisi A, Ferrari S, Mattei G, Pingani L, et al. Use and Propensity to Use Substances as Cognitive Enhancers in Italian Medical Students. Brain Sci. 2018;8(11). DOI: 10.3390/brainsci8110197.

2. Majori S, Gazzani D, Pilati S, Paiano J, Sannino A, Ferrari S, et al. Brain doping: stimulants use and misuse among a sample of Italian college students. J Prev Med Hyg. 2017;58(2):E130-E40. https://www.ncbi.nlm.nih.gov/pubmed/28900353.

3. Franke AG, Christmann M, Bonertz C, Fellgiebel A, Huss M, Lieb K. Use of coffee, caffeinated drinks and caffeine tablets for cognitive enhancement in pupils and students in Germany. Pharmacopsychiatry. 2011;44(7):331-8. DOI: 10.1055/s-0031-1286347.

4. Finger G, Silva ER, Falavigna A. Use of methylphenidate among medical students: a systematic review. Rev Assoc Med Bras (1992). 2013;59(3):285-9. DOI: 10.1016/j.ramb.2012.10.007.

5. Teter CJ, McCabe SE, LaGrange K, Cranford JA, Boyd CJ. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. Pharmacotherapy. 2006;26(10):1501-10. DOI: 10.1592/phco.26.10.1501.

6. Franke AG, Bagusat C, Rust S, Engel A, Lieb K. Substances used and prevalence rates of pharmacological cognitive enhancement among healthy subjects. Eur Arch Psychiatry Clin Neurosci. 2014;264 Suppl 1:S83-90. DOI: 10.1007/s00406-014-0537-1.

7. Liakoni E, Schaub MP, Maier LJ, Glauser GV, Liechti ME. The Use of Prescription Drugs, Recreational Drugs, and "Soft Enhancers" for Cognitive Enhancement among Swiss Secondary School Students. PLoS One. 2015;10(10):e0141289. DOI: 10.1371/journal.pone.0141289.

8. Wilms W, Woźniak-Karczewska M, Corvini PF, Chrzanowski Ł. Nootropic drugs: Methylphenidate, modafinil and piracetam - Population use trends, occurrence in the environment, ecotoxicity and removal methods - A review. Chemosphere. 2019;233:771-85. DOI: 10.1016/j.chemosphere.2019.06.016.

9. Jensen C, Forlini C, Partridge B, Hall W. Australian University Students' Coping Strategies and Use of Pharmaceutical Stimulants as Cognitive Enhancers. Front Psychol. 2016;7:277. DOI: 10.3389/fpsyg.2016.00277.

10. Maier LJ, Liecht, M. E., Herzig, F., Schaub M. P. To Dope or Not to Dope: Neuroenhancement with Prescription Drugs and Drugs of Abuse among Swiss University Students. PLoS One. 2013;8(11):e77967. DOI: 10.1371/journal.pone.0077967.

11. Smith ME, Farah MJ. Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. Psychological bulletin. 2011;137(5):717-41. DOI: 10.1037/a0023825.
12. Swanson JM, Wigal TL, Volkow ND. Contrast of medical and nonmedical use of stimulant drugs, basis for the distinction, and risk of addiction: comment on Smith and Farah (2011). Psychological bulletin. 2011;137(5):742-8. DOI: 10.1037/a0024898.
13. Marraccini ME, Weyandt LL, Rossi JS, Gudmundsdottir BG. Neurocognitive enhancement or impairment? A systematic meta-analysis of prescription stimulant effects on processing speed, decision-making, planning, and cognitive perseveration. Exp Clin Psychopharmacol. 2016;24(4):269-84. DOI: 10.1037/pha0000079.
14. Steward A, Pickersgill M. Developing expertise, customising sleep, enhancing study practices: exploring the legitimisation of modafinil use within the accounts of UK undergraduate students. Drugs (Abingdon England). 2019;26(4):347-55. DOI: 10.1080/09687637.2018.1555231.
15. Repantis D, Laisney O, Heuser I. Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: a systematic review. Pharmacol Res. 2010;61(6):473-81. DOI: 10.1016/j.phrs.2010.02.009.
16. Rossiter D, Blockman, M., Barnes K.I. South African Medicines Formulary 12th ed. Pretoria Health and Medical Publishing Group; 2016.
17. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4. DOI: 10.1001/jama.2013.281053.
18. Africa DoHRoS. South African Good Clinical Practice: Clinical Trial Guidelines. In: Health Do, editor. 3rd ed. Pretoria, South Africa 2019.

16. Appendix A

Dear participant

Hello, my name is Natasha Jurković and I am a registrar in the Department of Anaesthesiology at the University of the Witwatersrand. I am currently busy with my MMed research project entitled, **'Smart drug use in the Department of Anaesthesiology at the University of the Witwatersrand'**. The purpose of the study is to assess whether smart drugs are being used as aids to neurocognitive enhancement and what motivates this use.

I would like to invite you to participate in my study by completing the attached questionnaire. As a community service doctor, medical officer, fellow registrar or consultant your input is invaluable. This questionnaire should take approximately 10 to 15 minutes to complete. It is completely voluntary and your anonymity will be maintained. The information supplied in this questionnaire cannot be traced back to you. If at any point whilst completing this questionnaire, you should feel uncomfortable, you are free to withdraw from the study.

Should you have any questions regarding the study or questionnaire, kindly contact me. My contact details are supplied below.

Should you decide to participate, kindly complete the questionnaire, fold it in half and place it in the sealed boxes at the exit points of the venue.

Thank you for considering this study.

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0829655018

jurkovicn@gmail.com

Please select your answer by placing a cross in the relevant block. You may select more than one answer for certain questions.

1. Age
   - ☐ 23 - 30 years
   - ☐ 31 - 40 years
   - ☐ > 41 years
   - ☐ Prefer not to say

2. Gender
   - ☐ Male
   - ☐ Female
   - ☐ Non-binary
   - ☐ Prefer not to say

3. Are you currently employed as a
   - ☐ Community service medical officer
   - ☐ Post community service medical officer
   - ☐ Junior registrar (year 1-2)
   - ☐ Senior registrar (year 3-4)
   - ☐ Consultant (including principal medical officers)

4. Do you smoke cigarettes?
   - ☐ Yes
   - ☐ No

   4.1 If so
   - ☐ Daily
   - ☐ Occasionally
   - ☐ Only during stressful times
   - ☐ Socially

5. Do you smoke e-cigarettes?
   - ☐ Yes
   - ☐ No

   5.1 If so
   - ☐ Daily
   - ☐ Occasionally
   - ☐ Only during stressful times
   - ☐ Socially

6. Do you drink coffee?
   - ☐ Yes
   - ☐ No

6.1 If so

- ☐ Daily
- ☐ Weekly
- ☐ Sporadically

6.2 If so, do you do so

- ☐ Because I enjoy the taste
- ☐ To stay awake e.g. during calls
- ☐ To improve my concentration/attention/focus when studying
- ☐ Socially

7. Which of these do you drink?
   - ☐ Black tea
   - ☐ Green tea
   - ☐ Coca-Cola/Coca-Cola Energy
   - ☐ Caffeine-containing energy drinks e.g. Red Bull, Play, Monster, Reboost, Score, etc.

7.1 If so,

- ☐ Daily
- ☐ Weekly
- ☐ Sporadically

7.2 If so, I do so

- ☐ For work performance
- ☐ To stay awake e.g. during calls
- ☐ To improve concentration/attention/focus when studying
- ☐ For sports/gym performance
- ☐ Socially

8. Do you drink energy drinks that do not contain caffeine e.g. Powerade, Lucozade?
   - ☐ Yes
   - ☐ No

8.1 If so

- ☐ Daily
- ☐ Weekly
- ☐ Sporadically

8.2 If so, I do so

- ☐ For work performance
- ☐ To stay awake e.g. during calls
- ☐ To improve concentration/attention/focus when studying
- ☐ For sports/gym performance
- ☐ Socially

9. Have you ever heard of nootropics or smart drugs?
   - ☐ Yes
   - ☐ No

10. Have you ever heard of neurocognitive enhancement?
   - ☐ Yes
   - ☐ No

11. Please select which of these products you currently use/have used before
   - ☐ Ginkgo biloba
   - ☐ Caffeine tablets
   - ☐ Omega 3
   - ☐ IQ Boost (Vital)
   - ☐ AddVance
   - ☐ Concentration cocktail (Activo)
   - ☐ Exam cocktail (Activo)
   - ☐ KeenMind
   - ☐ Neuroactive (active ingredient piracetam)
   - ☐ Other (please specify)

     _____
     _____
     _____

11.1 If you use any of the above, do you do so
- ☐ Daily
- ☐ Weekly
- ☐ A few times a year
- ☐ I've only ever used it once

11.2 Have you used any of the above substances in the last 30 days
- ☐ Yes
- ☐ No

11.3 Do you use these medications
- ☐ During stressful periods
- ☐ For studying

12. Have you ever been diagnosed with attention deficit/hyperactivity disorder?
    - ☐ Yes
    - ☐ No

13. Have you ever used any of the following prescription medications
    - ☐ Strattera (atomoxetine hydrochloride)
    - ☐ Ritalin/Concerta/MPH HCl (methylphenidate)
    - ☐ Provigil (modafinil)
    - ☐ Aricept/Ariknow/Arimer/Donecept (donepezil)
    - ☐ Reminyl (galantamine)
    - ☐ Ebixa/Memor (memantine hydrochloride)

    13.1 If so, you did so because
    - ☐ I was prescribed it for a medical condition
    - ☐ To increase my concentration/focus/attention
    - ☐ To increase my work productivity
    - ☐ To stay awake
    - ☐ To lose weight
    - ☐ To experiment
    - ☐ To socialise/party/'fit in'
    - ☐ To improve my sports performance

    13.2 How often have do you use these medications?
    - ☐ Daily
    - ☐ Weekly
    - ☐ Monthly
    - ☐ At least once annually

    13.3 Have you used any of the above prescription medications in the last 30 days?
    - ☐ Yes
    - ☐ No

    13.4 Do you/have you used these prescription medications
    - ☐ During stressful times
    - ☐ During exam time
    - ☐ During times of physical fatigue/tiredness

    13.5 How did you take these medications?
    - ☐ Orally
    - ☐ Crushed and snorted
    - ☐ Smoked

☐ Intravenously

13.6 How did you obtain these medications?

☐ Prescribed by a specialist/GP
☐ Prescribed by a friend
☐ Prescribed by myself
☐ A few loose tablets from a friend/acquaintance
☐ A contact that distributes them
☐ Internet site

13.7 Had you used these medications previously e.g. at school or during undergrad?

☐ Yes
☐ No

13.8 Prior to taking these medications, did you do any research on them?

☐ Yes
☐ No

13.9 If so, what type of research did you do?

☐ Discussion with colleagues
☐ Discussion with family
☐ Discussion with GP or specialist
☐ Internet

13.10 Did you experience any of the following whilst taking them?

- ☐ Palpitations
- ☐ Mood changes
- ☐ Irritability
- ☐ Aggressiveness
- ☐ Agitation
- ☐ Confusion
- ☐ Tremors
- ☐ Hyperactivity
- ☐ Headache
- ☐ Hallucinations
- ☐ Euphoria
- ☐ Seizures
- ☐ Abdominal pain
- ☐ Anorexia
- ☐ Nausea
- ☐ Fever
- ☐ Other

_____
_____
_____
_____

14. Do you know of any friends or colleagues that have used the above medications for neurocognitive enhancement?
    - ☐ Yes
    - ☐ No

15. If you have never taken any of the above prescription medications, have you considered taking them in order to improve your studying or exam results?
    - ☐ Yes
    - ☐ No

15.1 If not, why not?

- ☐ I do not believe they work
- ☐ I do not need anything to improve my studying
- ☐ I am wary of side-effects
- ☐ I am wary of addiction potential
- ☐ I do not know enough about their use in neurocognition
- ☐ It is cheating
- ☐ Other

_____

16. If there were a hypothetical smart drug that was proven to improve neurocognition, without side effects or addiction potential, would you use it?
    - ☐ Yes
    - ☐ No

17. Do you ever use any substances to help you relax?
    - ☐ Yes
    - ☐ No

    17.1 If so, which of these have you used?
    - ☐ Alcohol
    - ☐ Sleeping tablets
    - ☐ Tranquilisers
    - ☐ Herbal preparations e.g. St John's wort, valerian
    - ☐ Cannabis
    - ☐ Other (please specify)

      _____
      _____
      _____

Thank you for participating in this study

Appendix 2

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr N Jurkovic
School of Clinical Medicine
Department of Anaesthesiology
Charlotte Maxeke Johannesburg Academic Hospital

E-mail: jurkovicn@gmail.com

CC: Supervisor: Drs J Kay and R Lockhat <drjonty@gmail.com>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/03/24

REF: *R14/49*

PROTOCOL NO: **M200108** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Smart drug use in the Department of Anaesthesiology at the University of the Witwatersrand*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr N Jurkovic

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200108

NAME: (Principal Investigator)	Dr N Jurkovic
DEPARTMENT:	School of Clinical Medicine Department of Anaesthesiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Smart drug use in the Department of Anaesthesiology at the University of the Witwatersrand
DATE CONSIDERED:	2020/01/31
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs J Kay and R Lockhat
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/03/24

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore reports and re-certification will be due early in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

26/03/2020

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix 3: Turnit In Report

0300671r:JurkovicMMedArticle.docx

ORIGINALITY REPORT

7%	6%	5%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	1%
2	wiredspace.wits.ac.za Internet Source	1%
3	eprints.mdx.ac.uk Internet Source	<1%
4	Submitted to UC, Irvine Student Paper	<1%
5	www.pure.ed.ac.uk Internet Source	<1%
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14	www.thieme-connect.de Internet Source	<1%
15	www.scilit.net Internet Source	<1%
16	Norbert Jaušovec, Anja Pahor. "Other Approaches: From Neurofeedback to Cognitive-Enhancing Drugs", Elsevier BV, 2017 Publication	<1%
17	Mingzohn Ellen Kaland, Wendy Klein-Schwartz. "Comparison of lisdexamfetamine and dextroamphetamine exposures reported to U.S. poison centers", Clinical Toxicology, 2015 Publication	<1%
18	C Zeijlemaker, S Moosa. "The prevalence of burnout among registrars in the School of Clinical Medicine at the University of the Witwatersrand, Johannesburg, South Africa",	<1%

	South African Medical Journal, 2019 Publication	
19	bmcmedicine.biomedcentral.com Internet Source	<1%
20	bpspubs.onlinelibrary.wiley.com Internet Source	<1%
21	Larissa J. Maier, Severin Haug, Michael P. Schaub. "Prevalence of and motives for pharmacological neuroenhancement in Switzerland-results from a national internet panel", Addiction, 2016 Publication	<1%
22	www.samj.org.za Internet Source	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Appendix 4

South African Medical Journal (SAMJ)

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.
To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website:
www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

Research
Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc.)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge

- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998; 289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

  - Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

Appendix 5

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

WITS UNIVERSITY

Department of Anaesthesia – University of the Witwatersrand

7 York Road, Parktown, 2193 South Africa • Telegrams "Witsmed" • Telephone (011) 488-4344 • Fax (011) 488-4343

Department of Anaesthesia
Area 361
Charlotte Maxeke Johannesburg Academic Hospital

Tel: 011 488-4344

8th October 2019

Subject: **Permission to conduct survey from Department of Anaesthesiology**

To whom it may concern,

This letter stands to affirm that I, Dr PMV Motshabi, grant permission to Dr Natasha Jurković HPCSA number MP 0300704, to conduct survey in Department of Anaesthesiology at University of Witwatersrand for her study "Smart drug use in the Department of Anaesthesiology at the University of Witwatersrand'.

The approximate period will be, but not limited to, the months of January 2020 to June 2020, until her sample size is obtained. The information obtained from the data will be used for Dr Jurković research study for her Masters in Medicine only, and will include information and data relevant to her study.

Yours sincerely,

WITS UNIVERSITY
Dr Palesa Motshabi
Academic Head: Department of Anaesthesia
Head of Clinical Unit: Cardiac Anaesthesia
Tel: +27 (0)11 488 4344
Cell: 083 432 1934
Email: palesa.motshabi@wits.ac.za
Website: www.wits.ac.za
WITS SCHOOL OF CLINICAL MEDICINE

Appendix 6: Strobe checklist

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for

		confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (e.g., average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other

		relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.