Ideologies of Intellect

A critical examination of the hype surrounding cognitive enhancement

Masters of Science (M.Sc.)

Lucie Wade

Department of Experimental Medicine, Specialization in Bioethics

McGill University

Montreal, Quebec, Canada

Jun. 13, 2011

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

DEDICATION

For Harpo.

ACKNOWLEDGMENTS

Many wonderful people contributed to my successful completion of this thesis. I would like to sincerely thank Dr. Eric Racine for his guidance and support over the past two years. His advice has been invaluable. In addition to Cynthia Forlini's encouragement and tremendous coding skills, this project would never have come to be if it had not been for her identification of the "cognitive enhancement trifecta." Dr. Emily Bell contributed generously through the editing of many drafts. And, of course, thanks go to Isabelle Chouinard and to Catherine Rodrigue for copy-editing and French language assistance.

I must also thank my committee members, Dr. Abby Lippman and Dr. Jennifer Fishman, as well as the members of the Neuroethics Research Lab and the Biomedical Ethics unit for their direction and advise during the early stages of my work.

Finally, thank you to Jamie Drooker, Emma Zimmerman, and my family for spending endless hours engaging me over the ideas put forth in this thesis, supporting me when the going was tough, and providing the inspiration needed to see it completed.

Financial support for the conduct of this research comes from the Institut de recherches cliniques de Montréal IRCM-Invitrogen Scholarship, a McGill University Provost Scholarship, the Fonds de la recherche en santé du Québec, and NeuroDevNet Canada.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES AND BOXES

LIST OF ABBREVIATIONS

CE: Cognitive enhancement

M: International print media

B: Interdisciplinary bioethics studies

DFSS: Donepezil flight simulator study

ID: Intellectual disability

FXS: Fragile-X syndrome

CONTRIBUTIONS OF AUTHORS

Task	Contribution
Review of the literature	LW 100%
Conceptualization of the project	LW 40%, ER 30%, CF 20%
Study design	LW 50%, ER 50%
Coding guide development	LW 70%, ER 10%, CF 20%
Initial Coding	LW 100%
Review of Coding	ER 30%, CF 70%
Content analysis	LW 85%, ER 10%, CF 5%
Development of results tables and figures	LW 95%, ER 5%,
Critical revision of tables and figures	LW 85%, ER 10%, CF 5%
Drafting of manuscript	LW 85%, ER 10%, CF 5%
Critical revision of the article	LW 70%, ER 20%, 10%

ABSTRACT

In the field of bioethics, the relatively recent phenomenon of cognitive enhancement—the idea that one might improve upon their typical, or "healthy," level of intellect through the use of pharmaceuticals developed to treat medical conditions—has garnered considerable interest from bioethicists and the popular media. The high level of coverage related to this phenomenon has prompted concern that a misrepresentation of the scientific facts related to the safety and efficacy of the drugs involved may encourage public interest, with potentially negative effects on social conformity and loss of diversity.

One drug in particular, donepezil, has become known as a "cognitive enhancement agent" based mainly on the findings of one small-scale study. Its genesis from contested Alzheimer's drug to revolutionary "smart-pill" has provoked questions related to the level of evidence driving this reconceptualization. Recent reviews have determined that the findings of the primary study were limited, and additional analysis of a possible link between donepezil and a cognitive enhancement effect have also found the study to be lacking.

This thesis characterizes how media and bioethics literature has shaped the discourse of donepezil as a cognitive enhancement agent in the absence of solid scientific evidence. A systematic content analysis was conducted to determine how media and bioethics articles portray donepezil and present the results of the landmark study. We found much hype of the possibility that donepezil could produce cognitive enhancement effects in typical individuals. Additionally, we identified a complex interaction between high expectations for a cognitive enhancement effect and ambiguous conclusions at the level of the primary paper. Together, these factors contribute to the portrayal of donepezil as a cognitive enhancement agent in secondary literature and point to important consequences for individual decision making, clinical care, and policy development.

Further, hype of the phenomenon of cognitive enhancement implies that there is general interest in the goal of increasing intelligence and inspires interest in further examining why we are so involved in this end. Propagating the ideology driving those captivated by cognitive enhancement may negatively affect people with intellectual

disabilities. To explore the connection between the desire to enhance cognition in typical individuals and a potential negative effect on people with intellectual disabilities, we introduce a distinct example of media hype related to drugs that target intelligence in this population. Failure to question the underlying assumptions that are driving the cognitive enhancement debate amongst individuals with typical intelligence risks further devaluing the lives of people with intellectual disability and subverting current social movements to empower these individuals and build a truly accepting and diverse society.

Keywords: Cognitive enhancement, donepezil, intellectual disability, neuroethics, public understanding of science, media, content analysis treatment-enhancement distinction

ABRÉGÉ

L'utilisation, par des individus sains, de médicaments pour améliorer leurs fonctions cognitives suscite l'attention autant des bioéthiciens que des médias. L'importante couverture médiatique de ce récent phénomène soulève la préoccupation qu'une fausse représentation des données scientifiques, relativement à la sécurité et à l'efficacité de ces médicaments, pourrait, par conséquent, éveiller l'intérêt du public. Potentiellement, cela pourrait causer des effets négatifs au plan social, par exemple, en encourageant la conformité et donc une perte de la diversité.

Un médicament en particulier, le donépézil, s'est vu reconnu comme étant un « produit d'amélioration des fonctions cognitives ». Cette affirmation est basée essentiellement sur les résultats d'une seule étude, marquante dans le débat entourant le donépézil. L'évolution de ce médicament, passant d'un traitement contesté pour la maladie d'Alzheimer à une « pilule d'intelligence » (ou *smart-pill*), a soulevé des questions relativement aux données probantes justifiant ce nouvel étiquette de « produit d'amélioration des fonctions cognitives ». Par ailleurs, des articles de revue de littérature ont récemment conclu que les résultats de l'étude en question sont limités, et le lien entre le donépézil et l'amélioration des fonctions cognitives n'est pas clair.

Le présent mémoire a pour objectif d'examiner comment la couverture médiatique et le débat bioéthique a influencé le discours sur le donépézil en tant que produit d'amélioration des performances cognitives, et cela, malgré l'absence de données probantes. Pour ce faire, nous avons procédé à une analyse systématique du contenu des médias et d'articles spécialisés en bioéthique afin d'examiner comment le donépézil et les résultats de l'étude y sont présentés. Nous avons identifié un enthousiasme débordant concernant la possibilité que le donépézil puisse améliorer les fonctions cognitives d'individus sains ainsi qu'une interaction complexe entre les attentes élevées et des conclusions ambigües au niveau de l'étude principale. Ensemble, ces facteurs ont contribué à la représentation du donépézil en tant qu'agent d'amélioration des fonctions cognitives dans la littérature et laissent supposer des conséquences importantes pour la prise de décision, les soins de santé et le développement de politiques.

L'engouement entourant l'effet du donépézil au niveau de l'amélioration des performances cognitives démontre un intérêt général par rapport à la possibilité d'accroître l'intelligence et confirme ainsi la nécessité d'un examen plus approfondi à savoir pourquoi un tel but est recherché. L'augmentation, au sein de la population, du désir d'accroître l'intelligence pourrait avoir comme conséquence de nuire aux personnes atteintes d'une déficience intellectuelle. Afin d'établir le lien entre le phénomène de l'amélioration des fonctions cognitives d'individus sains et l'effet négatif potentiel sur les personnes atteintes d'une déficience intellectuelle, nous présentons dans ce mémoire un exemple d'engouement des médias autour de médicaments qui cible l'intelligence chez cette population. Ne pas s'interroger sur les présomptions sous-jacentes qui motivent le phénomène de l'amélioration des fonctions cognitives chez des individus sains risque de causer plus de tort dans le débat du « traitement » de la déficience intellectuelle et de rendre impuissants les mouvements sociaux qui visent à améliorer l'acceptabilité sociale et à promouvoir la diversité au sein de la société.

Mots clés : amélioration des fonctions cognitives, donépézil, déficience intellectuelle, neuroéthique, compréhension des sciences par le public, médias, analyse de contenu de la distinction entre traitement et amélioration

INTRODUCTION

The appropriate dissemination of scientific knowledge in secondary literature, public or scholarly, has been identified as an area of concern for members of the public, researchers and policy developers alike. Evidence is mounting that misrepresentation of primary neuroscience studies in secondary discourses may have startling ramifications for public understanding and the development of social policy. Misrepresentation may also introduce practical problems at the level of clinical care and has the potential to influence the granting of research funds for certain projects over others [2, 4, 5]. In the field of bioethics the phenomenon of cognitive enhancement (CE), which has garnered considerable interest from bioethicists and the popular media, has drawn the additional concern that misrepresentation of science will encourage public interest in the phenomenon [6, 7], with potentially negative effects on social conformity and diversity [8].

This thesis explores how one pharmaceutical has become a subject of the CE debate and subsequently the focus of much secondary literature, both public and scholarly. Following the publication of a landmark study, the drug—donepezil—was widely heralded in both print media and interdisciplinary bioethics articles as a CE agent. The implication was clear: people felt the study demonstrated that donepezil could improve the cognitive ability of "healthy" individuals. However, recent reviews of the body of scientific evidence informing this notion have demonstrated that there is limited evidence of such an effect [9, 10]. We explore *how* media and bioethics literature have shaped the discourse of donepezil as a CE agent, as well as *why* this trend may have occurred. The goal of such research is to provide insight into the factors involved in disseminating neurological research within different discourses and to demonstrate how misrepresentation of primary literature has the potential to influence important policy, ethics, and clinical care decisions.

Understanding the genesis of donepezil as a "CE agent" requires a detailed understanding of the debate over what counts as CE versus what is accepted as medical treatment, a look at the power of the media and academia to frame this debate and an examination of the social pressure to enhance intellect and what that pressure may mean for the individual and society. Together, the case of donepezil reveals a demonstrable social interest for CE and the power behind it to sway researchers, bioethicists, and policy

analysts alike into conformity with this desire. This leads us to wonder, is social conformity the lone risk of CE? Or, by accepting this pressure to perform are we at risk of doing greater damage to individuals than we are currently accounting for? Are we idolizing intellect and intellectual ways of being to the detriment of other ways of being?

Chapter 1 provides a review of the relevant literature. It begins with an overview of the CE debate, the treatment-enhancement distinction, the role of medicalization, and scientific evidence related to efficacy and prevalence. We then explore the media's ability to shape public interest in scientific developments, with specific attention to the neuroscience and CE context. Finally, we introduce the landmark study this thesis focuses on (Yesavage *et al.* 2002) [11], and further describe our goals.

The methodological approaches used to conduct our empirical analysis of how the results of the landmark study [11] are presented in media and bioethics articles and how this presentation informs the perception that donepezil is a cognitive enhancement agent are described in Chapter 2. An explanation of qualitative content and discourse analysis is provided, along with a description of why this research style fits this project. We then provide more detail on the particular methods used, outlining how the use of systematic coding and Euler's diagrams allowed for the identification of misrepresentation and the analysis of accuracy in media and bioethics coverage of this case.

The results of our empirical study are presented in manuscript format in Chapter 3. This article, entitled, *Generating genius: a critical examination of how an Alzheimer's drug has become a "cognitive enhancer,"* includes detailed analysis of how media and bioethics articles, which reference the landmark study in their coverage of the CE debate, have characterized donepezil as a CE agent. Specifically, this manuscript examines media headlines and the titles of bioethics articles, as well as the colloquialisms used throughout the articles, to describe the messages conveyed regarding CE and donepezil. We also explore how the results of the study were reported in both literatures and assess the level of accuracy found in the reporting of the study characteristics. The paper concludes that far from being a simple case of misinterpretation or inaccurate representation of scientific studies by the media and bioethicists, the discrepancy apparent between media and bioethics articles' presentation of the study and what the scientific evidence provided by the study merits appears to be related to a complex interaction between the statements

made by the authors of the original study, the interpretation of these claims by journalists and bioethicists, and the presence of expectations and social pressure related to CE. By showcasing the high expectations for CE and the subsequent hype of CE effects present in these literatures, this manuscript demonstrates the power of the CE debate to influence individual actions, clinical care, and policy development.

To further explore the CE debate and its potential social implications, Chapter 4 considers the broad social forces shaping CE in light of a disability ethics perspective. We describe a related but distinct case of media hype regarding the possibility of increasing intelligence through novel pharmaceuticals; this time with respect to individuals with intellectual disability. Through this example, we explore the limitations of the treatment-enhancement distinction for discussing pharmaceuticals developed to treat cognition. We argue that the enhancement framework placed on donepezil has hyped the benefits of increased cognition, while the treatment framework—assumed appropriate for novel drugs for intellectual disability—precludes ethical deliberation of their effect on individual identity and well-being, and has the potential to undermine the current social movements that are working to empower people with intellectual disabilities. To this end, we conclude that neither the treatment nor the enhancement framework adequately accounts for the social context and intent that accompanies these drugs. To the contrary, both frameworks risk devaluing the lives of individuals with intellectual disability, potentially reducing social diversity and opportunity. Paying greater attention to the targeted effects of these drugs for individuals in light of their social and historical context, rather than focusing our attention on debating the ethics of enhancements as other to treatments, may help address these issues.

Our research demonstrates that there exists a widespread expectation that drugs for cognitive enhancement will be possible; however, it also explains that such expectations maybe be intricately related to social pressure. Not only will upcoming guideline and policy development regarding potential drugs for cognition need to determine whether reported efficacy is representative of a genuine effect, they must also consider whether the expectation and apparent desire for increased cognition is complicit with negative social norms.

CHAPTER 1 LITERATURE REVIEW

The concept of cognitive enhancement (CE) has inspired much debate amongst bioethicists, moral philosophers, and physicians. Simply understood, CE refers to the use of a medical intervention to increase an individual's intellectual ability above that which is typical to them. Far from being a value neutral term, referring to this increase as an *enhancement* establishes that the change is an improvement over the previous level of intellect [12]. This concept is sometimes referred to as "neuroenhancement" [9, 13], which "has been coined to denote interventions by which healthy people improve their cognitive, emotional and motivational functions" [9]; or, as "neurocognitive enhancement," "for improving the psychological function of individuals who are not ill" [14]. The medical interventions discussed most often with this concept are psychopharmaceuticals; however, medical devices may also be used (e.g., brain-machine interfaces and neural implants; see [15] for an overview). This thesis will focus on drug use and rely on the basic term "cognitive enhancement" (CE) for consistency. Setting these boundaries will focus our discussion towards the prevailing means of and intention to increase "cognition," as a general concept, which is often described without a discrete discussion of how its improvement would occur. To aid background understanding, it is currently accepted that cognition is an umbrella term for a "combination of skills, including attention, learning, memory, language, praxis (skilled motor behaviours), and so-called executive functions, such as decision making, goal setting, planning, and judgment" [16] that, if moderated, would increase overall cognition.

The concept of CE is fundamentally structured through its opposition to the common understanding of the role of medication. Referred to as "treatment," medication is usually viewed as a necessary tool to return or restore an individual to the level of functioning that is typical to them. As Daniels argues, "[c]haracterizing medical need… implies a contrast between medical services that treat disease (or disability) conditions and uses that merely enhance human performance" [17]. Alternatively, Jeungst describes enhancement technology as "designed to produce improvements in human form or function that do not respond to legitimate medical needs" [12]. It is important to note that this oppositional understanding of CE has not always been assumed. Indeed, original drugs developed to treat Alzheimer's disease, such as donepezil—an acetylcholinesterase inhibitor, were commonly referred to as "cognitive enhancers" [16] due to their action on

the cholinergic system, which is expected to be involved in memory [16, 18]. However, today the oppositional understanding delineating what is meant by the term CE is most common, especially for bioethicists [12].

A central argument in the bioethics literature is that this distinction is necessary due to a need to prioritize the use of medications in a resource-limited setting. Sabin and Daniels provide an established defense of this position arguing, "health care insurance coverage should be restricted to disadvantages caused by disease and disability" [19]. This model assumes the ability to distinguish what is a treatment from what is an enhancement through the use of a "normal function," [17] or "species-typical functioning," [17] standard. What counts as typical (read: medical) treatment is determined based on comparison across individuals; that is, to the functional abilities in an individual's "reference class," which is made up of those persons with similar age and gender [12]. The goal of such a description of what counts as medical treatment has been summarized as: "to secure for individuals a range of opportunities" [20], without providing treatment excessively where there is a natural difference rather than a medical one, i.e., "preserving differences…promoting the health of populations made up of people whose normal function takes different shapes" [20].

Another application of the treatment-enhancement distinction is to distinguish CE from the typical use of medication in order to emphasize the social role of enhancement technology. Within this faction, theorists define CE as "the amplification or extension of core capacities of the mind though improvement or augmentation of internal or external information processing systems" [21]. The concept of cognition is considered to represent these "processing systems" and can be discretely described and accessed by breaking it into four core capacities: perception, attention, understanding, and memory. Increasing any individual capacity is presumed to lead to an increase in overall cognition [21]. Theorists involved in this discussion see CE as a means for healthy individuals to improve upon their abilities, which will in turn create a better society for everyone. For instance, Sandberg and Bostrom strongly believe that cognitive ability is the greatest good to be had by an individual and by society; specifically, "[t]here are few resources more useful than cognitive ability…there is ample evidence that low intelligence increases the risk for accidents, negative life events, and low income, while higher

intelligence promotes health and wealth" [21]. They are, however, aware that "there is little evidence that high intelligence causes happiness" [21]. Instead, their glorified ranking of cognition relies heavily on Engelbart's idea that as the population increases, the economy increases and globalization occurs. Thereby, society's problems become more complex and urgent (see Engelbart 1962 in [21]). By increasing intellect, these theorists believe an individual will have greater ability to cope with the impending complexities described above, which, again, will be good for everyone.

A third camp has redefined CE as "cosmetic neurology" [22-24] (earlier described as "cosmetic psychopharmacology," by Kramer [25]), drawing a connection to cosmetic surgery as a way to explore, and often critique, the use of a medical technology for socially perceived reasons. This third group can be seen as a reflective group, bridging the two previous groups of thinkers by bringing the medical policy focus of the first to bear on the social good assumptions of the second by means of historical precedent.

Regardless of the camp one falls into when defining and discussing the phenomenon of CE—whether a theorist is concerned with the limits of the health care system, fundamentally believes that social betterment can be achieved through an increase in population intelligence, or is hesitant to use a medical technology for a social goal—the oppositional concept of CE that penetrates each stance has endured heavy critique on the grounds that the distinction between treatment and enhancement is contentious. A prominent concern is that the categorization of drugs (i.e., as treatment or enhancement) is highly dependent on social factors. Wolpe describes this trend stating, "what we consider disease intervention and what we do not… will conform to what the culture, or medical professionals, see as the proper objects of medical intervention" [26].

A second debate has also developed over the assumption of efficacy related to so-called CE agents. Within this debate, there is concern that pharmaceuticals said to increase cognition in individuals who fall into the treatment category do not have an effect on "healthy" individuals; yet, the rhetoric surrounding these drugs upholds the possibility. The following two sections outline how medicalization can affect the treatment-enhancement distinction and present the relevant literature in the assumption of efficacy debate, respectively.

Medicalization and the treatment-enhancement distinction

The utility of distinguishing what is classified as a treatment from what counts as an enhancement in order to provide access to a pharmaceutical has been questioned. A leading argument against this distinction is based upon the concept of medicalization. There is a risk that such a requirement will lead to the recasting of previously understood "enhancement" uses within a medical framework.

Historically, medicalization has been described as a "process whereby more and more of everyday life has come under medical dominion" [27]. Subsequent theorists, such as Conrad, have further articulated that medicalization is fundamentally a "definitional issue" [28] driven by the "sociocultural process" [28]. Thus, medicalization occurs when behaviour is defined "in medical terms, using medical language… adopting a medical framework… or using a medical intervention to "treat" it" [28]. While Daniels' argues, as outlined above, that we can draw a distinct line between the use of medications for individuals with a clearly recognizable disease and those without, Conrad counters: "what constitutes medical need is not self-evident and may differ by society and shift over time" [28]. Specifically, "[n]ew diseases or disorders may be defined (as diagnoses) in order to legitimize medical interventions" [28]. Thus, while the treatment-enhancement distinction seeks to clarify and restrict what is considered a treatment, the medicalization argument sees this task subverted as the oppositional nature of the dichotomy allows for states that were previously considered to be typical to be redefined as diseases or disorders and thus make their way into the accepted realm of treatable conditions.

Furthermore, the process of medicalization may have grave implications for society. As Conrad explains, sociologists have linked this process to social control, which can occur through therapeutic means "especially when individualism is highly valued" [28] by a society. As Conrad and Schneider point out, medicalization is thought to be enabling of social control because it provides the "authority to define certain behaviours, persons and things" (as cited in,[28]). This can be problematic for society if "the medical model decontextualizes social problems, and collaterally, puts them under medical control" [28]. Attempts to alleviate problems of the collective are limited to resolution by way of individual, medical, approaches; namely a technological solution to social

problems [28]. Another foreseeable problem associated with a sliding treatment-enhancement distinction is the possibility that framing the use of pharmaceuticals within a medical model will undermine the need to apply appropriate ethical oversight. Ethical issues relating to the use of drugs for "enhancement" purposes are wide-ranging and well documented. Recasting this use as a medical one does not remove these ethical considerations, but risks subverting their priority (see Box 1-1 for a list of well documented ethical issues that have been developed throughout the CE debate).

Box 1-1: List of ethical considerations related to the use of pharmaceuticals for cognitive enhancement purposes (adapted from [2])

Social integration and acceptability
Social meaning
Safety
Abuse
Cheating
Inauthenticity, identity and personhood
Injustice and inequalities
Over-prescription
Lack of autonomy, individual choice and informed consent
Illegality
Commercialization
Efficacy

To understand how medicalization can limit the utility of the treatment-enhancement distinction, introducing an element of social control into the equation, we must have sufficient background on the commonly considered types and categories of medical social control. Conrad outlines four types which, when present, contribute to the medicalization of a social phenomenon: Type 1) Medical ideology, the ability of medicine to provide an explanation for a behaviour; Type 2) Medical collaboration, the involvement of physicians to detect a behaviour, provide information, or act as gatekeepers to a medical intervention; Type 3) Medical technology, the use of a medical intervention to control behaviours or social phenomenon (i.e., the use of pharmaceuticals to combat sexual dysfunction or implement the death penalty); and, Type 4) Medical surveillance, where "physicians may legitimately lay claim to all activities concerning the

condition" [28]. By way of these types of social control, two general categories of behaviour are commonly medicalized: "deviant behaviour" and "natural processes" [28]. In the past, the "deviant behaviour" category has been employed to refer to homosexuality, alcoholism, and learning disabilities, while the "natural processes" category has referred to childbirth, menstrual discomfort and aging [28]. The following section of this review focuses on social control related to the medicalization of Alzheimer's disease and the aging process but, as pointed out by Conrad, "while the specific origins and consequences of each of these arenas of medicalization may differ, many of the issues are similar" [28].

Aging, Alzheimer's disease, and medical social control

The potential for the treatment-enhancement dichotomy to contribute to the medicalization of social phenomenon can be observed through the example of Alzheimer's disease and the drug donepezil.

Simply stated, managing memory loss in Alzheimer's disease with the drug donepezil is commonly referred to as a treatment use [24]. Consider this use as falling within category A. In contrast, providing donepezil to an unimpaired 60-year-old businessman so he can learn languages more quickly than his colleagues is usually considered an enhancement use [23]. Call this category D. Between categories A and D we can draw two intermediate examples. (There may, however, be an indefinite number of examples spanning the divide between these two categories. We only wish to point out that there is an on-going discussion of what that grey area might consist of and delineate that discussion by establishing reference categories.) Consider category C. The same 60-year-old businessman is experiencing some intermittent memory problems, forgetting his keys, mixing up names. Would providing him with donepezil be considered a treatment or enhancement use? What about category B; another 60-year-old businessman is said to be experiencing "mild cognitive impairment." That is, he has been that informed he has "mild cognitive deficits in one or more of the same domains but can function independently"[29]. Evidently, the context within which the drug is given is important. Yet, whether this context indicates it ought to be considered within the treatment or

enhancement categories may be highly dependent on the society and the degree of medicalization applied to the aging process therein.

Alzheimer's disease currently occupies a place in the *Diagnostic and Statistic Manual of Mental Disorders* [30] as a degenerative disorder and we would be hard pressed to find someone who does not consider it a disease state. However, "[Alzheimer's disease] itself represents a socially constructed label for the tail end of the distribution of age-related cognitive decline" [31]. It was not always so prominently pictured in society. Once "an obscure disorder" [28] used to describe senility in individuals below 60 years of age, removal of the age criterion for a diagnosis of Alzheimer's merged it with senile dementia. As a result, cognitive decline previously associated with senile dementia was recast "as a result of a specific disease rather than an inevitable aspect of aging" [28] though "the difference between normal and abnormal [is] quite arbitrary" [32] in this context. Currently, "no biological marker can definitively differentiate normal aging from [Alzheimer's disease]" [31]. In contrast to an understanding of dementia as part of the natural process of aging [31], this new definition introduces "medical ideology" and shifts it to the jurisdiction of medical social control (Conrad's Type 1). The implications of this medicalization of dementia for individuals and family members have been widely explored and may be both positive and negative, such as increased stigma or access to health care, respectively [32].

The genesis of the development and uptake of donepezil as a drug for memory demonstrates a further degree of the medicalization of Alzheimer's disease: as a medical technology it adds Type 3 medical social control. When donepezil (Aricept®) was first developed by Eisai Inc. and Pfizer as a drug to help restore memory loss in Alzheimer's patients [1] its use was questioned. Its applicability to Alzheimer's patients is dependent on the cholinergic hypothesis (see [33] for more detail related to this hypothesis): the idea that cognitive impairment in aging individuals is caused by "damage to the cholinergic neurons of the basal forebrain caus[ing] deficits in acetylcholine in the brain" [16, 18]. Acetylcholine is actively removed from the synapse by the enzyme acetylcholinesterase. The cholinergic hypothesis supports the idea that, by inhibiting the action of this enzyme, acetylcholine will remain present in the synaptic junction and memory will increase [18]. However, this theory remains to be proven. For example, though depletion in

acetylcholine is present in Alzheimer's disease, it is not isolated to Alzheimer's alone, introducing doubt that it plays a causal role; further, there are additional neurotransmitters involved in cognitive functioning, some of which are also impaired in Alzheimer's disease; and finally, studies have failed to consistently report a cholinergic deficit in the early stages of the disease [18].

In light of this applicability problem, it is not surprising that the original launch of donepezil for the purpose of treating Alzheimer's was met with controversy. Critics claimed "[n]o evidence to date indicates that donepezil improves the quality of life of patients with [Alzheimer's disease], nor is there any good evidence of the long-term efficacy and safety of donepezil" [34]. However, in 1997 it was approved by Health Canada for the treatment of mild to moderate Alzheimer's disease, becoming the first drug available for Alzheimer's patients [34, 35]. And, in 2007 Health Canada further approved its use for severe Alzheimer's disease [35]. However, the *National Institute for Health and Clinical Excellence* (NICE), the UK national health care authority, did not approve it until March of this year (after surviving a judicial review of its decision, which was based on cost-effectiveness) [36]. NICE still only approves its use for mild and moderate forms of Alzheimer's, yet this new ruling is predicted to have a significant influence on the management of Alzheimer's disease [37]. Recent meta-analysis research has determined that clinical studies do show benefits of donepezil on cognition and daily living activities, but also considers that "the effects are small and are not always apparent in practice" [3]. There are also many side-effects associated with its use (Box 1-2).

Box 1-2: Side-effects noted in the product monograph [1] as assessed by Birks and Harvey [3] in their meta-analysis

nausea*
vomiting*
diarrhea
muscle cramps
fainting/dizziness*
fatigue*
anorexia**

*Only increased risk on the highest does (10mg/day rather than 5)
**noted to be a significant risk in both the 5mg/day and 10mg/day groups

In addition to its heavily debated use as a treatment for Alzheimer's disease, there has been a further discussion about providing donepezil to individuals in category B (mild cognitive impairment), potentially shifting this category to more firmly reference a disease in need of a treatment. Individuals who fall into this category are already thought to use cholinesterase inhibitors, like donepezil, to improve their cognition [24] with even some Alzheimer's societies connecting the drug to mild cognitive enhancement [38]. This use medicalizes the experience of these individuals (Conrad's Type 3) and frames donepezil as a treatment. However, evidence that donepezil is efficacious in this population is lacking. As Birks and Flicker report in their publically accessible plain language summary, "[t]here is no evidence to support the use of donepezil for patients with mild cognitive impairment…The putative benefits are minor, short lived and associated with significant side effects" [39].

Of interest, the "descriptive term," [38] mild cognitive impairment is not officially a medical condition or diagnosis, "even experts are confused as to whether [it] is a diagnosis or just a label" [31]. However, it has recently been accepted into the upcoming DSM-5 [29]. The "description" will be refined as an Alzheimer's subtype: "Minor Neurocognitive Disorder" [29]. The presence of this new disease classification is interesting for many reasons; namely, because the term "mild cognitive impairment" was already a recasting of behaviours previously captured within the general concept of "age-associated memory impairment" [24], demonstrating the stepwise progression towards a medical conception of this set of behaviours (Conrad's Type 1). This description is especially fascinating as it "abstracts one portion of the human brain aging process and artificially creates its boundaries," [31] clearly depicting the construction of a novel disease state.

The predicted impact of the recasting of mild cognitive impairment is vast. Some experts claim the number of individuals who have mild cognitive impairment equals the number with dementia, some 5.4 million people [40]. This has implications for all individuals as they age. As Whitehouse has mused, "attempts to recognize early dementia have created a new world of people perplexed by their cognitive aging" [41], with many seeking medical interventions even in the absence of strong efficacy data, for what used to be considered typical to the life-cycle.

Returning to our original example, categories A and B are now commonly understood within the "treatment" category due to the process of medicalization. Categories C and D then remain as the only situations where we would refer to the use of donepezil as an "enhancement". However, considering the movement behind officially defining the diagnosis of mild cognitive impairment it is conceivable that individuals in category C may begin to fall more often into the treatment category. Furthermore, even if category C is managed in the same way as category D, it may still be medicalized to a degree. Consider, for example, that a phenomenon is usually medicalized by being discussed in medical terms, followed by the development of technology to address the newly defined problem [28]. With CE, the possibility of cognition being medicalized by first discussing it as a "condition" is excluded due to the very definition of enhancement (which places it outside the realm of medication). However, the means of CE relies on medical technology, thereby introducing Type 3 medical technological control. This degree of medicalization is particularly interesting. Though still considered outside the realm of medicine by bioethicists, it requires an assumption of efficacy of these drugs.

A closer look at this assumption demonstrates that claims of efficacy are often tied to the additional supposition of increased prevalence, and both seem to be fundamentally flawed. This leads us to wonder, is the distinction between CE and treatment sustainable? While at the same time asking, is CE even possible?

Cognitive enhancement and assumptions of efficacy and prevalence

It is commonly asserted that interest in the possible CE effect of pharmaceuticals began with the advent of modern antidepressants [42]. The frontrunner in this discussion was Prozac (fluoxetine), a selective serotonin reuptake inhibitor (SSRI) predicted to have a positive effect on the mood of healthy individuals [25]. Because SSRI's may also have an effect on motivation and cognition they received attention as potential cognitive enhancers [42]. Other drugs, such as psychostimulants, i.e., methylphenidate (Ritalin) have been more closely related to the CE debate (e.g., [10, 14, 43, 44]). In 2009, one study found 14 bioethics articles made a specific connection between methylphenidate and CE [2]. Methylphenidate is thought to improve cognition by increasing executive function through an improvement in attention and working memory [45]. It is assumed to

be “useful for enhancing studying and work… especially in the context of high-stress situations such as academic testing” [5], and has been strongly associated with college students [46, 47]. Modafinil (Provigil), developed to treat sleep disorders, has also been linked to the phenomenon of CE (e.g., [10, 45].

However, establishing that CE occurs when healthy individuals take these drugs has proved to be challenging. A review of the effects of anti-depressants on healthy subjects concluded that “no consistent evidence of an enhancing effect” [42] can be established. A subsequent review by the same group covering studies on methylphenidate and modafinil concluded that no conclusion could be drawn regarding the effect of methylphenidate on healthy individuals. The current body of data “provides insufficient evidence for or against any effect” [48] and includes many studies that show “inadequate result reporting” [48]. Modafinil was found to have “moderate, enhancing effects on individuals who were not sleep deprived, namely on attention” [48]. However, “[n]o effect was found on memory, mood, or motivation” [48].

Less comprehensive examinations of the body of studies on the effects of methylphenidate on healthy individuals have also pointed to the difficulty of establishing efficacy based on this body of knowledge. For example, Outram has remarked: “problems with compatibility of study outcomes and the limited number of studies on specifically healthy population groups make it difficult to reach conclusions about the enhancing capabilities of this drug in real world situations” [49]. Lucke *et al.* also describe the difficulty in determining real world effects. Specifically, they question “whether statistically significant improvement in cognitive function can be translated into practical or clinically significant benefits in real-world contexts” [7]. Moreover, there is evidence that the degree to which a pharmaceutical increases cognition may be influenced by the baseline ability of the consumer [50]. And, though methylphenidate might improve certain faculties on novel tasks, such as executive function, there is evidence that it “impairs previously established performance” [51]. Concerning the question of whether so-called CE drugs actually have a CE effect, we appear to have a hung jury, calling into question the widespread discussion surrounding the use of these drugs for CE purposes. Indeed, critics have recently given the prominent bioethics discussion surrounding CE the label “the phantom debate” [6].

However, interest in the phenomenon of CE may have less to do with objective knowledge of efficacy than with the perception of efficacy as it relates to widespread use [48]. That is, these drugs may be presumed efficacious due to the appearance of prolific use for CE purposes. Indeed, bioethics literature related to CE converges over the idea that there has been an increase in the prevalence of individuals practicing CE. Consider the argument of a prominent neurologist who chaired the American Academy of Neurology's (AAN) committee on this topic: "[i]n the last decade alone there has been an increase in neuroenhancement to the point that at least one-third of students at some colleges have used such drugs illegally" [52]. However, these claims of increased use are undermined when close examinations of the bodies of evidence they reference are considered.

Due to methodological differences amongst the oft-cited sources of statistical data it is difficult to compare estimates of prevalence to establish the current or changing size of the market [49]. Some claims of prevalence have even been made without reference to secondary literature or empirical studies [5]. Lucke *et al.* have found that many estimates of prevalence rely on: 1) anecdotal evidence or convenience samples, which are not statistically sound research methods; 2) sales estimates for pharmaceuticals compared to the estimated number of individuals with the medical diagnosis the drug is licensed to treat, which overlooks the prescription of these drugs to individuals who either do have medical indications yet or whose indications may not have warranted a formal diagnosis; and, 3) the assumption that the majority of illegal and unprescribed pharmaceutical use is for the purpose of increasing cognition rather than for recreational use (i.e., experiencing a "high"), which has not been established [6, 7]. In fact, one investigation of studies that explored the reasons individuals were motivated to use methylphenidate found a high prevalence of recreational use, overriding or approximating its use as a study aid [49]. Finally, the most recent investigation of the prevalence of use of pharmaceuticals associated with CE concluded that demands have not increased in recent years, rather they are "equivocal" [5]. Clearly, in addition to its presumption of efficacy the CE debate assumes the practice is prevalent; however, this secondary assumption too remains unproven.

Recently, the perception that CE drugs are both efficacious and in demand has been used as impetus for the development of regulatory frameworks to govern drug use for CE purposes. For example, based on the view that "[n]eurocognitive enhancement is already a fact of life for many people" and the prediction of "a growing number of people practicing neurocognitive enhancement in the coming years" [14] Farah concluded that "[t]he question is therefore not whether we need policies to govern neurocognitive enhancement, but rather what kind of policies we need" [14]. Others, like the UK Academy of Medical Sciences, have argued for establishing authorities to regulate the use of CE agents (as cited in [48]). Such endorsements have been reflected in the publication of three reports by professional associations and governmental bodies [5]. All three publications, from the British Medical Association [53], the Commission de l'éthique de la Science et de la technologie du Québec [54], and the AAN [55], cited increasing demand and predictions of increased efficacy of available pharmaceuticals as their rationale for paying specific attention to the phenomenon of CE [5].

The AAN's policy guidelines are particularly intriguing. They focused on developing guidelines to deal with requests from patients for CE agents. By accepting the efficacy and prevalence of pharmaceuticals presumed to have a CE role and using an established medical association to develop and implement these guidelines, the AAN has further medicalized the concept of cognitive enhancement. Now, in addition to being Type 3 medicalized because it uses pharmaceuticals, it is also Type 2 medicalized because it uses "medical collaboration" [28]. Thus, in spite of little to no scientific evidence of efficacy or increased prevalence we have continued medicalization of a phenomenon that is supposedly outside the medical realm.

Why this phenomenon has come to exist at this level with this limited body of evidence is a provocative question. Previous research has shown that the media may play a role in the dissemination of information related to this phenomenon that might drive interest and misrepresent the level of evidence. Certainly, precedent exists for thinking that the media play a role in the dissemination and public understanding of science [56]. Yet, academia has also been implicated in driving misinformation in the public sphere [57]. The following section explores the current evidence linking misrepresentation of the

CE debate to the media, as well as the potential for academia to play a part in perpetuating misleading information.

Cognitive enhancement and the influence of the media and academia

The assumption that the phenomenon of CE is currently possible and the subsequent attention paid to it by national and medical organizations, clinicians, researchers and the public may be influenced by print media coverage of the phenomenon.

Extensive research has drawn attention to the general role the media play in raising public awareness of scientific research. In her book entitled, *Selling Science*, Nelkin outlines how the media can shape public understanding of the risks and benefits of scientific developments, impacting public acceptance of scientific advances and influencing policy. The media provide a "framework of expectations," [56] defining isolated scientific events in such a way that they can be interpreted by individuals and "take on meaning as public issues" [56]. Public acceptance of the ideas put forward in the media seems to be related to a portrayal of scientific research as having direct clinical benefit through "immediate applications, promising solutions… effective new therapies" [56]. These "promises of future technological marvels" [56], which may be based on "speculat[ions] about the futuristic implications of contemporary research" [56], often reflect uncritical representations of science "as the ultimate source of authority" [56]. Further, the use of imagery and metaphor in media coverage creates "judgmental biases," [56] related to the potential of the scientific advance. Indeed, the selection of what scientific research is covered in the media itself works to define an event as "newsworthy" [56] or "pressing" [56]. This judgmental framework may be seen as a function of the concept of news itself. The news by definition has to be "novel, unprecedented and recent" [58]. And science news must compete with all the other news genres, e.g., politics, economics, and sports, to earn coverage; that is, it has to "shout to be heard" [59].

As a result, the coverage of science by the media acts to "create the reality and set the public agenda" [56] for new developments in science and technology. It has the potential to either positively or negatively influence public understanding of science and

society at large. Negative news coverage can greatly decrease public interest in a product, while positive coverage can launch a technology into the forefront of consumer interest [56].

The field of neuroscience is also subject to both the positive and negative effects of the media [60]. Potential positive influences include the reduction of stigma by increasing public awareness of the biological basis of mental illness [61]. However, negative effects seem to be more widespread in this field. As Illes and colleagues explain, neuroscience is particularly prone to misinformation and inaccuracy in reporting due to the complexity of the research and the implicit connection between neuroscience research and society [62]. Individuals perceive neuroscience research as highly relevant due to "the neurological basis of individual and social behaviour" [62] as well as the connection to widely recognized devastating brain disorders. Neuroscience combines this high individual and social relevance with rapid advances in technologies, creating an opportunity to greatly influence public acceptance [62].

Specific trends in media coverage of neuroscience relate to the media's ability to shape public acceptance of and expectations for new technology. Namely, by providing overly optimistic portrayals of the clinical benefits of neuroscience advances, through sensational headlines and terms or by failing to report important details, risks, or limitations of a study or technology, misinformation is spread and expectations are increased [60, 63-66]. It is common for even experimental technologies to be associated with clinical benefits, often through speculation or by portraying the post-intervention symptoms as preferable to those of the previous medical condition, regardless of what they may be [60, 64].

An early surgical intervention resulting from neuroscience research was lobotomy. Diefenbach *et al.*'s account of the media's coverage of this intervention demonstrates the media's power to influence public opinion and drive medical implementation [64]. To begin, medical opinion opposed the performance of lobotomy, however, the media overwhelmingly presented uncritical, misleading (if not inaccurate), and optimistic accounts of the benefits of this intervention. Between 1935 and 1945, lobotomy became widespread, despite medical warnings that it should only be used as a last resort option. From 1945-1960 media reports became more balanced, and even

critical, yet a few high profile articles continued to present sensational, risk-free, and misrepresentative accounts of the benefits of the surgery. Innovation leading to modification of the technique used in this procedure also encouraged new articles, keeping the practice in the public eye and continuing to drive its use. Finally, in the late 1950's the practice ceased when its perceived utility was replaced by less invasive pharmaceutical treatment [64]. Subsequent research on novel neurosurgical interventions has demonstrated that similar miracle portrayals of the experimental technology by the media can act to increase pressure to develop and approve them [65].

A further role of the media has been realized with respect to the field of neuroscience in general: it has the potential to fuel controversy by shaping and perpetuating misinformation in high profile ethical debates and to mislead individuals in the decision-making process. For example, one study of the role of the media in the public understanding of chronic disorders of consciousness and end-of-life decisions, specifically the Terri Schiavo case, demonstrated that the media contained both inaccurate claims and charged language [67]. Potentially damaging policy discussions, such as a challenge to proxy decision-making, were influenced by these media reports [67]. Further, the reports introduced the possibility for mistrust between family members and their physicians as they were challenged to disregard the information presented by the media and trust the advice of their medical team [67]. Of greatest concern, the reports introduced false hope of a full recovery, exacerbating the decision-making context [67].

Within the field of neuroscience, the propagation of misinformation by the media has also been connected to the CE debate; specifically, to the discussion of methylphenidate. Recent neuroethics research has connected media coverage of methylphenidate use amongst university students to shaping or perpetuating the idea that the drug is a safe, effective and accepted cognitive enhancer. As Racine and Forlini demonstrate, the media often present the effects of drug use for CE with overt optimism or sensational language [2, 68]. For example, by evoking metaphors such as "miracle drug," the media inaccurately project the idea that "non-medical prescription use is a safe and acceptable practice" [68], even a "laudable goal" [2]. Media descriptions of the drug as a "study too[l], just like tutors and caffeine pills" [68] that can yield "better living" [68] portray social acceptance and perpetuate the idea that drug use will help individuals

"be all that they can be" [2, 68]. This encourages public acceptance of the practice as such anecdotes do not reflect the "reality of research" on efficacy (specifically, that which shows limited support of an enhancement effect) [2]. Indeed, after reading several media reports, students reported that they thought using these drugs should be an (unregulated) individual choice [2].

Additionally, the discrete terms used by media articles to frame drug effects have been found to influence the acceptability of CE. For example, a study of the psychology driving the demand for CE found that study participants were reluctant to use drugs for the enhancement of traits they identified as "fundamental" to their self-identity [69]. Kindness and social comfort were ranked as more fundamental than traits like foreign language ability and concentration. Further, when the effects of the drugs were framed differently, i.e., as "enabling" rather than as "enhancing", there was an increased (significantly) willingness of the study participants to use the drug to change even a fundamental trait [69].

An examination of the role of the British media in the discussion of the non-medical use of modafinil has also demonstrated an inadvertent form of media influence on social acceptance. In contrast to the above discussed media reports lauding the potential of methylphenidate for non-medical use, the British media overwhelmingly presented concern, "if not outright condemnation" [70], with the idea of non-medical, life-style or performance enhancing use of modafinil. However, the media was shown to be a "key way…of mediating a pharmaceutical to the public" [70], especially in a country where direct to consumer advertising is prohibited. In fact, the authority of medicine was described as being "'reworked' or 'reconfigured'" [70] in media coverage. Thus, though highly critical of non-medical use, it was posited that media coverage of such a possibility could inadvertently facilitate CE use by "diffusing information and raising awareness" [70]. Speaking to the general coverage of the possibility of CE drugs, Lucke *et al.* support this conclusion, arguing, "misplaced concern about the putatively widespread occurrence may have inadvertently advertised its possibility" [6]. Additionally, media coverage may increase interest in CE by suggesting that the phenomenon is widespread when prevalence is probably low [7].

Evidently, media coverage of the phenomenon of cognitive enhancement, combined with its reliance on anecdotes in place of scientific fact [2] and tailored or sensationalist language, can lead to misinterpretations of the phenomenon and could contribute to the propagation of non-medically approved practices that have poorly understood consequences [2, 68]. This potential for media misrepresentation may be seen as distinct from scientific publications which are not necessarily concerned with presenting "new things but about how relatively newish evidence either fits into existing frameworks of knowledge or adapts existing theory" [58]. However, other research has shown that some instances of media hype of scientific information cannot be totally accounted for by inaccurate reporting on the part of the media [58, 71].

The potential for media to contribute to hype has also been discussed as being symptomatic of a larger trend—that of scientists and other stakeholders contributing to the misrepresentation of the effects of a specific technology. Research communities, funding agencies, and patient groups may also play a role in the propagation of misinformation. An interaction between these parties and the media, referred to as a "spatial dynamic," [58] can create "the progressive accumulation of expectations around otherwise quite abstract bits of data and knowledge" [58]. Thus, misinformation or speculation might not be isolated or caused by the media. This trend has been noted in science in general by Rose who argued that media hype was less a problem of inaccuracy than it was of uncritical presentation of novel scientific advancements. Rather than being inflationary, the media may be too deferential to claims made with the authority of science [59]. This becomes problematic when scientists are unable to articulate that "most of the time [they] are dealing not with certainties but with uncertainties" [59], and instead lean too heavily on speculation. Indeed, a recent study by Gonen *et al.* reports that overstatements of therapeutic effect found in media articles seem to have been "faithfully reported" [4] from the conclusions of the scientific articles themselves. Thus, it was not media speculation, misinterpretation, or spinning that led to the presence of misleading information. Rather, authors of primary studies were responsible for the misrepresentation [4].

The idea that a misrepresentation of scientific fact may implicate both the media and academia has already been linked to the phenomenon of CE. A commentary

considering how methylphenidate has become a primary example of the potential for CE has concluded that it has less to do with empirical evidence than it has to do with media and academic speculation over the ability of these drugs to change lives [49]. Such speculation seems to have introduced "a cycle of expectation" regarding how subsequent research and media reports frame discussions of what these drugs are capable of in such a way that even detailed discussions of the limitations of scientific research on their efficacy are unsuccessful at curtailing speculations and subsequent calls for regulation [49].

Research objectives

This review of the literature shows a discrepancy between the level of evidence supporting the concept of CE and the interest that the phenomenon continues to garner. What is known about the potential of the media to shape the debate around CE, combined with the potential for academia to contribute to the public perception of this phenomenon inspires a need for further insight into what is currently driving the perception that CE is possible. With this in mind, this thesis explores how the drug donepezil, discussed above, has recently come to be known as a CE agent.

The case of donepezil

In this thesis we explore the case of donepezil, examining how it has become swept up in the CE debate. Specifically, we characterize how donepezil has recently emerged in both print media and interdisciplinary bioethics literature as having CE effects, becoming the third drug listed in what has been coined the "cognitive enhancement trifecta" [72], following methylphenidate and modafinil. While the concept of CE has garnered particular interest from bioethicists and the popular media—and, as noted above, the genesis of methylphenidate as a CE agent has been explored in detail (e.g., [2, 73, 74]; the use of modafinil for this purpose has also generated significant interest from individuals outside the CE debate [70, 75])—the interest of both these literatures on the drug donepezil as a CE agent has been especially remarkable. Particularly given its contested use in the shifting medical sphere as a treatment for various age-associated

"diseases". Yet nothing, to our knowledge, has been written about how donepezil came to be seen as a CE agent.

A recent review by Repantis *et al.* reported on six scientific studies that have been conducted to determine whether donepezil has an effect on nominally healthy individuals [9]. After careful review of the findings of each of these studies the authors concluded that scientific evidence of a CE effect was "lacking. Regarding the use of [acetylcholinesterase inhibitors]… the available data do not allow to draw firm conclusions… the few existing studies… provide no consistent evidence for a neuroenhancement effect" [9]. Included in this review was a study by Yesavage *et al.*, entitled, *Donepezil and flight simulator performance: Effects on retention of complex skills,* which measured the effect of donepezil on pilot performance in a flight simulator (see Box 3-1 in Chapter 3 for further study details; [11]). This study in particular has been widely cited as evidence that donepezil can enhance cognition; accordingly, it is the focus of our analysis. From here on we will refer to it as the donepezil flight simulator study (the DFSS).

In specific reference to the DFSS, the Repantis *et al.* review is only able to conclude the limited, and specific, finding that "donepezil *might* improve the retention of training on complex aviation tasks" ([9], emphasis added). A previous research study examining the results of the DFSS in light of several other studies also argues, "the available evidence does not appear to support the widely cited conclusion that donepezil improves the retention of training" [10]. Of interest, in a response to a commentary written after their paper was published the authors of the DFSS made an even more explicit statement regarding the limitations of their results: "[o]ur results should not be interpreted as a recommendation for the use of donepezil as a drug to improve flight performance" [76]. Yet, in spite of these admonishments, the study has remained a landmark reference in the CE debate; used as support for the claim that donepezil is a potential CE agent.

Indeed, a media and academic search found 27 media articles and 22 bioethics articles written between 2002 and 2009 that cite the DFSS as evidence for a CE effect (see Chapter 3 of this thesis). Even the recent guidelines of the AAN included donepezil in their list of potential CE pharmaceuticals and cite the DFSS as support for this claim

[55]. Also citing the DFSS, others have argued that school children, as well as professionals such as pilots and surgeons, should have access to CE pharmaceuticals [43, 77-79]. Based on the Repantis *et al.* review and the earlier work of de Jong *et al*. these media and bioethics reports appear inaccurate. However, the factors contributing to this apparent discrepancy are not clear.

How did this small study become a key reference in the CE debate? Considering the purpose of the study, this question becomes even more salient. The authors hypothesize that "an acetycholinesterase inhibitor would affect simulated flight performance," based on the prior claim that "[p]iloting an aircraft requires a range of cognitive and psychomotor skills, many of which are *affected by aging*" ([11]; emphasis added). This undermines the presumed purpose of the study as it is widely cited within the CE debate, that is, to determine whether the drug may have a CE role. As discussed above, the concept of aging blurs the treatment-enhancement distinction. The presentation of aging in the DFSS, as something one is affected by, also frames it as a disease requiring treatment, more than a typical state to be improved upon (the typical state becomes that of the individual as a young adult and the typical states of the future-aged individual are seen as deviations from this norm). This idea is supported by the author's description of the "Age-60 Rule" as one of the reasons for conducting the study, a rule that prohibits pilots from flying once they reach 60 years of age [11]. To an extent, their methods also reflect this "aging-as-a-disease to be ameliorated by donepezil" purpose. They tested nondemented individuals, ruling out a focus on Alzheimer's disease, and their average test participant was 52.5 years old, somewhat addressing an interest in "older" pilots and ruling out an interest in the effect on college test takers. Yet, they limit the insight that their study could have provided to a discussion of the "Age-60 Rule," explaining in their discussion section that their study was not really designed to test this ("because of the need to avoid "ceiling effects," the flight tasks learned in this experiment are more difficult than those experienced in routine flight operations" [11]). The reader is left to ponder what this study *was* designed to test.

It appears that what we can take away from the DFSS is that when a group of nine individuals with an average age of 52.5 years, who may or may not be suffering the effects of aging—which is identified as a strong possibility through the implementation

of the “Age-60 Rule”—are given donepezil, they performed the second test better than the nine individuals of the same age who were not given the drug. Understood in this way, relating information from this study to the CE debate that specifically focuses on the use of drugs for category D enhancement suddenly becomes very illusive.

Evidently, the mere presence of this study in the CE debate raises questions. Its further presentation as support for a CE effect appears irresponsible. Yet, as the study continues to be referenced in popular and academic literature it continues to contribute to the general hype regarding the prospects of CE for individual and social betterment, the ethical imperative to address related moral issues, and the development of policy to confront practical problems.

This thesis characterizes how media and bioethics literature has shaped the discourse of donepezil as a CE agent, examining what factors might account for the presentation of an interpretation of the DFSS in popular and scholarly articles that is not merited by analysis of the study itself. Do these reports reflect inaccurate reporting of the study by the media and bioethicists? Do they reflect the interplay of a larger “spatial dynamic” [58]? We address these questions in both media and bioethics literatures.

CHAPTER 2 METHODS

The goal of this study was to characterize how international (including Canada, US, UK) print media (M) and interdisciplinary bioethics (B) articles have shaped the discourse of donepezil as a cognitive enhancement (CE) agent. We investigated how both literatures report the findings of one empirical study, the donepezil flight simulator study (DFSS; Yesavage et al. 2002 [11])—which examined the effect of donepezil on aging pilots in a flight simulator—and analyzed the connections that are made between the results of the study and the CE debate.

Sampling

To generate our print media sample, we searched the *Factiva* academic database. *Factiva* is a Dow Jones product, designed to facilitate access to up to date business information from top news sources [80]. It acts as a searchable source of archived and current full-text news reports from newspapers, magazines and wires. We searched for English language articles published between 2002 and 2009, inclusively, to capture media articles released following publication of the DFSS in 2002 [11]. We used guided news search options, searching general interest publications, major news and business publications, news digest publications, newspapers, wires, and top news page sources, to maximize coverage and used multiple key-word searches to broadly identify articles that addressed cognitive enhancement, donepezil, and the DFSS [63, 81]. The terms "donepezil", "Aricept", "E2020", "acetylcholinesterase", "enhance", "Yesavage", "Mumenthaler", "Neurology", "pilots", "flight simulator", "memory", "illicit drugs", "study aid," and their variants were used in different search combinations to maximize relevant results. Our search was saturated when continued variations of key word searches were performed, yet no novel articles were found. Initial searches yielded 339 potential articles. To develop our bioethics sample we performed citation searches in the academic databases *Pubmed, Google Scholar, Medline*, and *Proquest.* A total of 137 articles (7, 85, 21, 41, respectively) were identified that specifically referenced the DFSS.

Articles were excluded from our samples if they were duplicates, referenced a different study by the same authors, focused on the medical use of donepezil (e.g., Alzheimer's, schizophrenia, bipolar, mild cognitive impairment, impaired attention, dementia), or referred to the study in the wider context of animal research. For the

bioethics sample, non-peer reviewed and non-English language publications, as well as articles published after 2009 were also excluded. Inclusion criteria were then applied, restricting our samples to only include articles that discussed CE. The media sample was further examined to ensure that each article either made direct reference to the DFSS or made indirect reference to the study by presenting at least four study characteristics (e.g., year, journal, author, author affiliation, subjects, methods, results, limitations, ethical issues raised) that clearly established its identity. Our final sample included 27 international print media articles and 22 interdisciplinary bioethics papers (Appendix 2-1 and 2-2).

Content and discourse analysis

To characterize how reporting of the DFSS in media and bioethics articles has contributed to the widely-cited idea that donepezil is a cognitive enhancement agent, we applied content analysis to all media and bioethics articles. Content analysis can be either quantitative or qualitative. The style that is chosen designates how categories are generated and applied to the data, as well as how the resulting data set is analyzed [82]. Performed quantitatively, content analysis is defined as "the systematic, objective…analysis of message characteristics" [83]. The quantitative approach is best for objectively gathering and sorting discrete, "informational content" [82]. In contrast, a qualitative approach to content analysis involves "open-ended data collection techniques aimed at detail and depth, rather than measurement" [82].

We used qualitative content analysis for our study since we needed a methodological approach that allowed us to explore the meaning behind the terms that were used to discuss donepezil, as well as to convey the findings of the DFSS. The exploratory and theoretical approach of the qualitative method has been successful in providing "a comprehensive description of a phenomenon" [82] and "understanding processes" [82] in previous empirical bioethics studies. Specifically, it allows researchers to "examine and challenge bioethical assumptions, inform clinical practice, policy-making or theory" [82], all of which are in line with the goals of this study. Most importantly, a qualitative approach allows one "to understand a phenomenon, rather than to make generalizations…based on statistical inference" [82]. By using a qualitative

approach to content analysis, we were able to describe the information related to donepezil that was conveyed in media and bioethics articles, and contrast it against that found within the DFSS itself. Such an application of content analysis reflects previous research conducted on the portrayal of neuroscience and genomics in the media, as well as on press coverage of CE specifically [2, 63, 84].

Since we were examining both media and bioethics articles, and were comparing how the results of the DFSS were informing the CE debate, we also carried out a discourse analysis. Discourse analysis is used to qualitatively "typify [text] representations," [83] of ideologies that surround a phenomenon and are being presented to the public [75]. To this end, rather than examine the coded text at the level of the individual article, our analysis was carried out within a discourse (media or bioethics) and focused on exploring the implications of and meaning behind language and word use [83]. We analyzed the language used by both discourses to discuss donepezil, as well as to report the study characteristics and findings of the DFSS, and contrasted it with that found in the DFSS itself. This type of analysis has been previously used in studies examining the representation of modafinil in the media [70, 75] and methylphenidate in media, bioethics, and public health discourses[2]. In our case, using a discourse analysis provided a means of comparing between discourses, i.e., between media and bioethics articles, or media and the DFSS, as well as within discourses, i.e., medically, or in the language of the CE debate, allowing us to determine what messages were being conveyed about donepezil and where.

Coding

The content of all sample articles was systematically coded using either the QSR NVivo 8 software (Doncaster, Australia), for complex coding, or Microsoft Excel, for simpler tasks. To facilitate and guide the systematic analysis of articles, a coding guide was developed. Our coding guide was inductively generated based on previous content analysis of media coverage of CE [2] but was adapted to reflect the goals of this project, that is, to capture all information conveyed that was related to the DFSS. Extensive pretesting on a sub-set of ten print media articles was conducted to ensure the coding "nodes" (discrete categories used to organize the material) were robust enough to

adequately reflect the information provided in the articles. After one author (Lucie Wade; LW) conducted the initial round of pretesting, two other authors (Cynthia Forlini and Eric Racine; CF and ER) reviewed the nodes to ensure external validity (i.e., to confirm that the themes described by LW were also apparent to the co-authors). LW then conducted initial coding of all articles. Once coded, a co-author (CF or ER) reviewed the coding and a third party (ER or CF) resolved any disagreements over challenging codes. This process of establishing consensus about the selected themes ensured that though our coding guide was developed through an appeal to our existing ideas about the literature, we could be confident that it was reliable enough to be extended to cover all the articles in our sample. Completed in this way, we could be rigorous without loosing the level of subjectivity that is expected (as our goal is to show how we interpreted the literature).

Our final coding guide allowed for systematic analysis of content related to three distinct aspects of each article: (1) headlines and titles; (2) colloquialisms used to refer to donepezil; and, (3) reporting of the characteristics and results of the DFSS. Headlines and titles were separated from the body of the articles and coded based on two major areas: 1) whether they claimed an enhancing property; or 2) if another effect or theme was conveyed. Sub-themes of the "enhancement" node covered what property, if any, was reported, whether pharmaceutical use was discussed and how the context of cognitive enhancement was portrayed (i.e., if they suggest that CE is currently happening, is anticipated, or is undesired). Sub-themes of the "other" node covered the main property or subject of the alternative effect or theme conveyed (Appendix 2-3).Coding headlines and titles independently was important to establish the general message conveyed to the reader within an article. Further, headlines are often selected by the editor of the paper, rather than the journalist responsible for the piece, and may reflect the editor's perception of what would make an exciting headline, or a headline that would "sell". As such, they may offer a stronger claim than what is found in the body of the article, impacting the overall message conveyed.

Colloquialisms, or lay terms, used to refer explicitly to donepezil were also coded independently. To ensure connection with the DFSS, colloquialisms were coded only if they were found within the paragraph where the DFSS was referenced; or, in bioethics articles, if there was a direct structural connection to the reference (i.e., the colloquialism

was found in the heading of the section where the study was referenced). Colloquialisms were coded with respect to the effect they imply (Appendix 2-4).

Finally, media and bioethics articles were systematically coded to capture how they conveyed the results, qualifying clauses and study characteristics of the DFSS. Only information that was clearly linked to the reference of the DFSS found in each bioethics and media article was retained for coding. The specific coding guide applied to the reporting of the DFSS identified: (1) general study information, such as the authors and journal of publication; (2) the characteristics of the study (e.g., sample size, subject information, tests used, dosage information); (3) statements of the results or findings of the study broken into two levels: "specific" results (i.e., an explicit statement of the results of the study) and "extended" results (i.e., when the author of the article interpreted or restated the "specific" results to introduce the study, or to connect it to wider issues); as well as reports of qualifying clauses related to the rigor or limitations of the study (Appendix 2-5). The DFSS was also coded using the coding guide applied to both media and bioethics articles.

Once the material was coded, basic descriptive statistics were used to report the content found within each code. This allowed us to explore the frequency and distribution of each code within each discourse, providing a measure of what content was emphasized where and was adequate for the initial analysis of the headlines and titles, colloquialisms, and results reported [83]. However, our analysis of the reporting of study characteristics required a more specific analytical method.

Specific analysis of study characteristics by Euler's circles

Our goal was to rigorously compare the study characteristics described in the DFSS with those reported in the media and bioethics articles. Specifically, we were interested in determining how accurately reports of the characteristics of the DFSS found in media and bioethics articles reflect those of the study itself. To provide a measure of accuracy, we needed an objective system that would allow for comparison of a secondary claim (those of the media and bioethics articles) against a primary claim (those found in the DFSS). By comparing the two claims, we hoped to determine the relationship between them, which would provide insight into the accuracy of media and bioethics reporting. Euler's

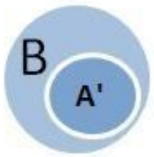
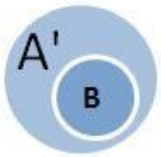
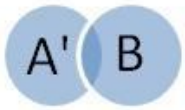
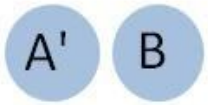
circles, a basic form of logical analysis, provided us with the rigorous approach we needed.

Euler's circles provide a clear, discrete and easily replicated method for the logical analysis of how closely a claim relates to or represents another claim. As a diagrammatic system, it allows one to affirm "simple intuition" [85] regarding the relationship between two terms because it can be "easily conceptualized" [85] by visual inference [85]. The visual clarity that is offered in this system of analysis is lost if more than two claims are being compared [85]; however, since we only wish to examine two terms, this method was sufficient.

Using Euler's circles, logical analysis was conducted by dividing the secondary claims into five distinct logical classes, called categorical proposition classes, which each represent a different relationship between the primary and secondary claims and act to "affir[m] or den[y] that a class [*B*; secondary] is included in a class [*A'*; primary]" ([86]; Box 2-1). A class is considered as "the collection of all objects that have some specified characteristic in common" [86]. Thus, by applying this technique to our sample, we were able to determine accuracy by demonstrating the various ways that claims put forward by media and bioethics articles, which each reflect a class of objects, may be related to the claims, and associated classes, found in the DFSS.

Media and bioethics reports of study characteristics were identified as B (claims; B) and actual study characteristics as A'. Claims made by media and bioethics articles were placed in the proposition class that best reflected their relationship to the A' characteristic. This analysis was initially performed by LW and was reviewed by ER. The distribution of claims between proposition classes and categories of study characteristics was then calculated on a one article per category basis (even if that article made more than one distinct claim), yielding a basic unit of analysis we refer to as an "article-claim" (see the legend of Table 3-5 for further detail). In this way, we were able to examine how many article-claims fell into each categorical proposition class and determine how the majority of claims made in media and bioethics articles represented the study characteristics listed in the DFSS, as well as gaining insight into what categories of study characteristics created representational challenges.

Box 2-1: Categorical proposition classes designated by Euler's circles. Each proposition class represents a different relationship between the claim made in the primary study (the DFSS; A') and the corresponding claims made within media and bioethics articles (B).

Class of Proposition				
				
Same Class (same or synonyms)	**A:** ***All A' are B*** (B is an overstatement, generalization)	**Reverse of A:** ***All B are A'*** (B is a specification)	**IO:** ***Some A' is B, some A' is not B*** (variable)	**E:** ***No A' is B*** (mutually exclusive classes)

CHAPTER 3 RESULTS

Generating genius:
A critical examination of how an Alzheimer's drug has become a "cognitive enhancer"

Lucie Wade,[1,4] Cynthia Forlini,[1,3] Éric Racine,[1,2,3,4]*

Affiliations
1. Neuroethics Research Unit, Institut de recherches cliniques de Montréal
2. Department of Medicine and Department of Social and Preventive Medicine, Université de Montréal
3. Departments of Neurology and Neurosurgery, McGill University
4. Division of experimental Medicine and Biomedical Ethics Unit, McGill University

*** Corresponding author**
Eric Racine, PhD*
Director, Neuroethics Research Unit and Assistant Research Professor, Institut de recherches cliniques de Montréal
Department of Medicine and Department of Social and Preventive Medicine, Université de Montréal
Departments of Neurology and Neurosurgery, Medicine and Biomedical Ethics Unit, McGill University

Institut de recherches cliniques de Montréal
110 avenue des Pins Ouest
Montréal, QC H2W lR7
Tel: (514) 987-5723
Email: eric.racine@ircm.qc.ca

Acknowledgements
Support for the conduct of this research comes from the Institut de recherches cliniques de Montréal IRCM-Invitrogen Scholarship (LW), a McGill University Provost Scholarship (LW), the Social Sciences and Humanities Research Council (SSHRC, ER), the Fonds de la recherche en santé du Québec (FRSQ, CF, LW), and NeuroDevNet Canada (ER). We would like to thank members of the Neuroethics Research Unit, Dr. Abby Lippman, and Dr. Jennifer Fishman for feedback on previous versions of the manuscript. Thanks also to Dr. Ralph Jox for providing generous insight into the case study.

Abbreviations
The Yesavage et al 2002 study will be referred to as the Donepezil Flight Simulator Study, the DFSS; international print media articles as M; interdisciplinary bioethics articles as B; and, cognitive enhancement as CE.

Abstract

Background

Donepezil, an acetylcholinesterase inhibitor designed to treat Alzheimer ’s disease (AD), has been widely cited in media and bioethics literature as having the potential to improve the cognitive ability of healthy individuals (cognitive enhancement; CE). In both literatures, this claim has been widely supported by the results of a singly study (Yesavage *et al.* 2002) despite recent evidence suggesting that donepezil is not a proven CE agent. The factors contributing to this apparent discrepancy are unclear. We examine the nature of media and bioethics coverage of this landmark study, aiming to provide insight into how evidence from neurological research may be shaped within different discourses, potentially influencing important policy, ethics, and clinical practice decisions.

Methods

Examination of the reporting of this study in print media and interdisciplinary bioethics literature was conducted using systematic content analysis. 27 media articles and 22 bioethics papers were analyzed for content related to three distinct categories: (1) headlines and titles; (2) colloquialisms used to refer to donepezil; and, (3) reporting of the characteristics and results of the landmark study. In this final category we examined how the results were put forward and whether the study characteristics were reported accurately.

Results

Our analysis demonstrates that both media and bioethics articles conveyed very high expectations regarding the use of donepezil for CE. The majority of headlines, titles, and colloquialisms used enhancement language and suggested that donepezil could be used to improve intellectual ability. Analysis of the reporting of the results of the primary study showed that ambiguity within the primary study regarding the interpretation of the results was reflected and subsequently magnified in media and bioethics reports. Specific descriptions of the results of the study overwhelmingly reported an improvement in performance on a flight simulator, while more general statements claimed donepezil enhanced cognitive performance. Finally, our analysis of the reporting of study characteristics showed a high level of accuracy when characteristics were clearly presented in the original study, but variable levels of accuracy for complex characteristics (i.e., methods) or for contentious properties of the CE debate (i.e., the initial health status of the subjects). As a result, the high expectations of CE effects we found associated with donepezil cannot be completely accounted for by simple inaccuracy in reporting.

Conclusion

Both media and academic literature often hype the limited conclusions that can be drawn from basic research, putting them in line with expectations that may be heavily influenced by prominent social pressures. A complex interaction between the authors of primary and secondary literature, and widespread expectations and social pressures, appears to drive this phenomenon. Mediation of such an interaction will require the development of (1) translation programs to evaluate and appropriately disseminate the knowledge produced by individual studies, as well as (2) guidelines to address social pressure at the level of clinical care. Failure to do so may have implications for patients and consumers as they attempt to evaluate the veracity of claims and make informed decisions.

Background

In 2002, a paper published in the journal *Neurology* reported an effect of donepezil (an acetylcholinesterase inhibitor) on the ability of non-demented pilots to retain complex skills in a flight simulator (Yesavage *et al.* 2002 [1], from here on referred to as the Donepezil Flight Simulator Study, DFSS; see Box 1).Subsequently, media and bioethics articles have cited this study as evidence that drugs can be used to increase cognitive function in healthy individuals (cognitive enhancement; CE), informing a public and academic debate on the development of CE agents for use by professionals or school children [2-5]. In 2009, guidance for neurologists from the American Academy of Neurology on how to respond to requests for "neuroenhancement" also cited the DFSS, suggesting that donepezil can "improve memory and executive function" [6]. However, a 2010 review of studies on the effects of acetylcholinesterase inhibitors on healthy populations, including the DFSS, concluded that there is insufficient evidence to support CE claims made about donepezil [7]. The factors that have contributed to this apparent discrepancy between the findings of the review and the claims of secondary literature are unclear. However, as the study continues to be referenced the depiction of donepezil as a CE agent is propagated, calling into question the veracity of claims made in media and bioethics literature which may inform policy.

This study aims to inform how donepezil has been shaped as a cognitive enhancement agent through an examination of media and bioethics coverage of the DFSS. Further, we seek to provide insight into how evidence from neurological research may be shaped within different discourses, potentially effecting important policy, ethics, and clinical practice decisions.

Box 3-1: Brief overview of the DFSS [1].

In 2002, Yesavage *et al*. 2002 conducted a study on 18 pilots, aged 30-70 with a mean age of 52, who were split into placebo and control groups. The groups were randomized, and after seven 75 minute long practice tests on a flight simulator (where the baseline for the study was also calculated), the drug group was administered 5mg of donepezil per day for 30 days. On day 30 both groups performed two more flight simulator tests. The primary outcome measure of the study was the change in flight score from the flights performed on day 30, when compared with those on day zero. Four different flight components were assessed during the flight simulations: communication, traffic avoidance, emergencies, and approach to landing. The results of the study state: "flight performance of the pilots in the donepezil group changed little from performance after the initial training to 30-day post-treatment… whereas it declined in pilots in the placebo group" (see Table 2 for a more detailed description of the results).

Methods

This study analyzes the reporting of one study, the DFSS, in public and academic literature. We conducted a systematic review of international (i.e., including Canada, US, UK) print media (M) and interdisciplinary bioethics literature (B) where references to the DFSS appeared within a discussion of CE.

Sampling

We searched the *Factiva* academic database using key word searches to find English language media articles on CE published between 2002 and 2009, inclusively, based on existing media sampling methods [8, 9]. The start date was selected to capture media articles released following the publication of the DFSS. Key word searches were used to broadly identify articles that addressed cognitive enhancement, donepezil, and the DFSS. The terms "donepezil", "Aricept", "E2020", "acetylcholinesterase", "enhance", "Yesavage", "Mumenthaler", "Neurology", "pilots", "flight simulator", "memory", "illicit drugs", "study aid," and their variants were used in different search combinations to maximize relevant results. Initial searches yielded 339 potential articles. To develop our bioethics sample we performed citation searches in the academic databases *Pubmed, Google Scholar, Medline*, and *Proquest.* A total of 137 articles (7, 85, 21, 41, respectively) were identified that specifically referenced the DFSS.

Articles were excluded from our samples if they were duplicates, referenced a different study by the same authors, focused on the medical use of donepezil (e.g., Alzheimer's, schizophrenia, bipolar, mild cognitive impairment, impaired attention, dementia), or referred to the study in the wider context of animal research. For the bioethics sample, non-peer reviewed and non-English language publications, as well as articles published after 2009 were also excluded. Inclusion criteria were then applied, restricting our samples to only include articles that discussed CE. The media sample was further examined to ensure that each article either made direct reference to the DFSS or made indirect reference to the study by presenting at least four study characteristics (e.g., year, journal, author, author affiliation, subjects, methods, results, limitations, ethical issues raised) that clearly established its identity. Our final sample included 27 international print media articles and 22 interdisciplinary bioethics papers.

Content analysis

A coding guide was developed to guide the systematic analysis of articles. The coding guide was inductively generated based on previous content analysis of media coverage of CE performed by two of the authors (CF and ER; [10]). Extensive pretesting on a sub-set of articles was conducted to tailor this previous coding guide to the specific research objectives of this project. The coding strategy was "rich" and not mutually exclusive. Systematic analysis of content captured information related to three distinct categories within each article: (1) headlines and titles; (2) colloquialisms used to refer to donepezil; and, (3) reporting of the characteristics and results of the DFSS. One author (LW) was responsible for conducting the initial coding. One co-author (CF or ER) reviewed the coding and the other (ER or CF) resolved any disagreements over challenging codes. Complex coding was conducted using the QSR NVivo 8 software (Doncaster, Australia) while simpler components of coding were carried out in Excel spread sheets.

Analysis of headlines and titles

Headlines and titles were separated from the body of the articles and coded based on 1) whether they claimed an enhancing property; 2) what property, if any, was highlighted;

and, 3) how the context of cognitive enhancement was portrayed (i.e., if they suggest that CE is currently happening, is anticipated, or is undesired).

Analysis of colloquialisms

Colloquialisms, such as "smart pill" (Table 3-1; [11]), which were used to explicitly refer to donepezil, were coded independently. To ensure connection with the DFSS, colloquialisms were coded only if they were found within the paragraph where the DFSS was referenced; or, in bioethics articles, if there was a direct structural connection to the reference (i.e., the colloquialism was found in the heading of the section where the study was referenced). Colloquialisms were coded with respect to the enhancement property they imply (e.g., CE in general or memory specifically).

Analysis of result claims, qualifying clauses and study characteristics

Media and bioethics articles were systematically coded to capture how they conveyed results, qualifying clauses and study characteristics. Only information that was clearly linked to the reference of the DFSS found in each bioethics and media article was retained for coding. The specific coding guide applied to the reporting of the DFSS included the identification of: (1) the characteristics of the study (e.g., sample size, subject information, tests used, dosage information); (2) statements of the results or findings of the study broken into two levels: "specific" results (i.e., an explicit statement of the results of the study) and "extended" results (i.e., when the author of the article interpreted or restated the "specific" results to introduce the study, or to connect it to wider issues); and, (3) qualifying clauses related to the rigor or limitations of the study. The original study was also coded using the coding guide used for both media and bioethics articles. Descriptive statistics were used to quantify and qualify the distribution of headlines, titles, colloquialisms, and claims made about the results of the DFSS within the different codes, as well as qualifying clauses.

Specific analysis of study characteristics by Euler's circles

Logical analysis by Euler's circles was applied to reports of the characteristics of the DFSS found in media and bioethics articles to examine how accurately they reflect those

of the study itself. Euler's circles provide a clearly visible and easily replicated method for the logical analysis of how closely a claim relates to or represents another, primary, claim [12]. Logical analysis is conducted by division of secondary claims into five distinct logical classes, called proposition classes, each representing a different relationship between the primary and secondary claims (see Table 3-5 for proposition classes) [12, 13].

Media and bioethics reports of study characteristics were identified as B (claims; B) and actual study characteristics as A'. Claims made by media and bioethics articles were then placed in the proposition class that best reflected their relationship to the A' characteristic. The distribution of claims between proposition classes and categories of study characteristics was then calculated on a one article per category basis (even if that article made two distinct claims), yielding a basic unit of analysis we refer to as an "article-claim" (see the legend of Table 3-5 for further detail).

Results

Headlines and titles

To assess the main themes conveyed to readers of articles that cite the DFSS, we analyzed the media headlines and bioethics titles. The most common topic portrayed by media headlines was a general claim of an enhancement effect (N=18/27; 67%), which was almost always related to the use of a pharmaceutical (N=17/18; 94%). The majority of these headlines related the enhancement effect to intellect or cognition (N=9/18; 50%; e.g.,*Brain-boosting drugs could soon become the smart choice*[14]) or stated that an enhancement effect was currently possible (N=14/18; 78%) or anticipated (N=2/18; 11%; e.g., *Memory drug has landed*[15]).Few headlines presented wary or sceptical comments (e.g., *Can taking a pill make you brainy?* [16]). Within the headlines that did not focus on intellect or general cognition, enhancement effects on memory, attention, youth, or performance were conveyed.

Of the nine headlines that did not present an enhancement effect, the majority claimed that there had been a breakthrough for memory problems (N=6/9; 67%), and the majority of these headlines connected the breakthrough to medical use (N=4/6; 67%), while half specified that the breakthrough was pharmacological.

Most titles of the bioethics articles (N=16/22; 73%), featured the term "enhancement;" the majority specifically referring to "neurocognitive enhancement" (N=11/16; 69%). Bioethics titles generally suggested a more philosophical or critical approach to the issue of CE than media headlines did, but they still implied that CE was a possibility as they introduced the potential for concern, (N=10/16; 63%) e.g., *Neurocognitive enhancement: what can we do and what should we do?*[17]. In contrast to the media headlines, only 19% (N=3/16) of bioethics titles related enhancement to pharmaceutical use.

Additional themes in the bioethics titles were: 1) the role of medicine with respect to CE (N=8/22; 36%); mainly, the implications of the sliding treatment-enhancement scale, though two articles focused on the possibility of cognitive enhancement for physicians; and, 2) the progress or evolution of CE and appropriate responses for the future (N=6/22; 27%). None of the titles in our sample implied medical use of pharmaceuticals.

Colloquialisms

To determine whether explicit connections were made between donepezil and CE, we examined the colloquialisms that were used to refer to donepezil. Colloquialisms were used in 52% of media articles (N=14/27) and 45% of bioethics articles (N=10/22; Table 3-1) to refer to donepezil as a CE agent, with a total of 20M and 12B enhancement colloquialisms used. The majority of colloquialisms used enhancement language (N=10/20M, 50%; N=11/12B, 92%). A large proportion of both media and bioethics colloquialisms that used enhancement language specifically referred to cognitive or brain enhancement (N=4/10M, 40%; N=8/12B, 73%, e.g., "brain-enhancing drugs" [18, 19]). Additionally, many colloquialisms referenced an effect on intelligence though they did not use explicit enhancement language. When combined with those that referred explicitly to cognitive enhancement, 50% of media and 75% bioethics colloquialisms conveyed an effect on intelligence (N=10/20M, N=9/12B).

A minority of colloquialisms specified an effect on memory (e.g., "memory enhancing pills" [11]), youth, and safety. Two bioethics articles claimed the general

effect of enhancement, without specifying what characteristic or properties are enhanced (e.g., “enhancements” [20]).

Table 3-1: Colloquialisms used in media and bioethics discourses that explicitly refer to the drug donepezil*. The type of effect implied divides the terms.

	Media	Bioethics
Cognitive / Brain Enhancement	"the new ‘cognitive enhancers’" [21] "brain-enhancing drugs"[19] "brain-enhancing drugs"[18] "mind-enhancing medicine" [21]	“cognitive enhancement drugs”[22] “enhancers of cognitive performance”[23] “cognition enhancers”[24] “cognition enhancers”[25] “brain-enhancement drugs”[26] “neuroenhancement drugs”[27] “psychological enhancements”[28] “‘magic potions’ to enhance our ‘wisdom’”[29]
“Smarts”	"so-called ‘smart drugs’" [30] "so-called smart pills" [14] "smart pill"[11] "the 'older' smart drugs”[16] "the existing smart drugs”[16] “cognition drugs"[31]	“smart drugs”[29]
Memory Enhancement	"memory-enhancing drugs" [32] "memory-enhancing pills"[11] "Alzheimer drug boost for healthy memory"[33] "memory-enhancing medications"[34]	“memory enhancing agents”[29]
Others	"performance-enhancing drugs" [32] "the safety-enhancing drug" [21] "these 'fountain of youth‘ drugs" [32] “new brain boosters"[35] "brain cosmetics" [36] "a memory pill" [37]	“currently available enhancers”[38] “enhancements”[20]

*Or group of drugs containing donepezil.

Reporting of the results of the DFSS

To determine how the results of the DFSS were reported in media and bioethics discourses, we summarized the claims made in the primary study (Table 3-2), as well as those found in media and bioethics articles (Table 3-3 and 3-4).

The DFSS

In its abstract, the DFSS claimed that donepezil had “beneficial effects on retention” as pilots who took donepezil “showed greater ability to retain the capacity to perform”

(Table 3-2). In the results section, a significant difference was described between the drug and control groups related to "in flight performance change." Here the authors clarified that "flight performance of the pilots in the donepezil group changed little, whereas it declined in pilots in the placebo group" (Table 3-2). No mention of improvement in performance was claimed (the authors accurately referred to "differences in performance" and specific "drug effects" instead) until the discussion. At this point the authors stated that their results were consistent with previous studies' that "reported that cholinesterase inhibitors improve cognitive performance" (Table 3-2). They also extrapolated a connection between cholinesterase inhibitors, working memory and memory performance (Table 3-2).

Table 3-2: All statements of the results of the DFSS as they appear in the different sections of the study itself.

	Findings of the DFSS
Abstract	"After 30 days of treatment, the donepezil group showed greater ability to retain the capacity to perform a set of complex simulator tasks than the placebo group, p 0.05." "Donepezil appears to have beneficial effects on retention of training on complex aviation tasks in nondemented older adults."
Results	"After 30 days of treatment, there was a significant difference between the donepezil group (n=9, mean age 51.2 years) and the placebo group (n= 9, mean age 53.1 years) in flight performance change (F 6.1, p 0.05, effect size 0.58)" "Overall, flight performance of the pilots in the donepezil group changed little from performance after initial training to 30-day post-treatment (0.06 z-score units; SD 0.31), whereas it declined in pilots in the placebo group (0.24 z-score units; SD 0.19)" "To help focus the discussion of the likely locus of drug effects, post hoc analyses of flight component difference scores were computed. These scores reflect differences in performance between treatments over the course of treatment. Examination of the figure suggests the largest effects of donepezil were on the emergency scanning (effect size 0.56) and the approach to landing scores (effect size 0.52)"
Discussion	"Given the extensive literature on the effects of acetylcholinesterase inhibitors on memory, we were not surprised to find some effects of the drug on ability to retain a practiced skill in pilots" "Nonetheless, these results are consistent with previous studies in nondemented adults that have reported that cholinesterase inhibitors improve cognitive performance." "The association of cholinergic drugs with better attention has lead investigators to suggest that part of the benefit of cholinergic drugs on memory performance may be mediated through attentional components involved in working memory. This suggestion is supported by the current data that show the strongest drug effects on emergency tasks and the approach to landing. The emergency tasks involve visually scanning the instrument panel for aberrant readings. The approach to landing requires sustained divided attention to maintain proper altitude, speed, and heading"

Media and bioethics articles

All media and bioethics reports of the results of the DFSS, save one bioethics article, enthusiastically portrayed a beneficial effect of donepezil. The lone bioethics critique occurred at thelevel of *extended* results where the article expressed concern that: "the available evidence does not appear to support the widely cited conclusion that donepezil improves the retention of training" [38].

Specific results

Reporting of *specific* results was high (N=23/27M, 85%; N=18/22B, 82%; Tables 3-3 and 3-4), yielding a total of 36M and 19B specific results claims. Improvement

language was used in 94% of media claims (N=34/36M) and 84% of bioethics claims (N=16/19B). Of those claims that used improvement language, improved task performance by the pilots who took donepezil was mentioned in 71% of media and 63% of bioethics claims (N=24/34M; N=10/16B), mainly referring to their performance in the flight simulator and emergencies; memory performance was mentioned in 29% of media claims and 25% of bioethics claims (N=10/34M; N=4/16B); and brain performance was mentioned in only 6% of bioethics claims (N=1/16B)

Explicit enhancement language (i.e., the term enhancement or a variation on that term) was used in 3% of media claims and 11% of bioethics claims (N=1/36; N=2/19). The media claim that used enhancement language referenced brain performance, while both bioethics claims referenced task performance.

Extended results

The majority of articles also reported *extended* results (N=16/27M, 59%; N=13/22B, 59%; Tables 3-3 and 3-4), yielding a total of 23M and 14B extended results claims. Improvement language was used in 65% of media claims (N= 15/23M) and 36% of bioethics claims (N=5/14B). Of those claims that used improvement language, improved task performance by the pilots who took donepezil was mentioned in 33% of media and 20% of bioethics claims (N=5/15M; N=1/5B); memory performance in 33% of media claims and 40% of bioethics claims (N=5/15M; N=2/5B); and brain performance in 33% of media claims and 40% of bioethics claims (N=5/15M; 2/5B).

Explicit enhancement language was used in 30% of media claims and 50% of bioethics claims (N=7/23; N=7/14). Enhanced memory was referenced in 57% of media claims and 43% of bioethics claims (N=4/7M; N=3/7B); brain performance was referenced in 43% of media claims and 57% of bioethics claims (N=3/7M; N=4/7B).

Table 3-3: Statements of the results of the DFSS as reported in media articles. Reported findings are divided by effect on performance, memory, and brain, mind or mental capacity, and are further divided by how those effects are presented. The results presented in M and B were also divided into two levels, specific results (black) and extended results (red).

	Task Performance	Memory	Brain, Mind, Mental Capacity
Enhancement	---	"has turned out to enhance memory and concentration in healthy people" [33] "could lead to a memory pill" [37] "the success of the pilots' study does demonstrate that memory-enhancing pills are possible" [11] "Even memory enhancement seems within reach, at least for older folks." [39]	"was shown… to enhance mental performance"[35] "It is one of three prescription medications… that have been shown to enhance certain mental powers. The other two are… and donepezil."[19]; [18] "drugs investigated for their mind-enhancing properties include donepezil"[40]
Significant	"performed significantly better" [32]❶ "reportedly performed significantly better" [41]❶ "performed significantly better" [15]	"were significantly better at recalling"[30]❶❺	"Studies have shown that these drugs can produce significant mental gains in normal, healthy subjects." [19]; [18]
Non Specific	"was successfully tested"[37]	---	"The era of "brain-doping" may be looming."[33]
Specific	"Overall, pilots who took the drug showed little difference in performance ... The performance of those who took a placebo declined" [32]	---	---
Improvement + Superlative	"were measurably better able to perform" [11]❶❷ "especially excelled" [34]❸❹ "did markedly better" [42]❶❸❺ "performed markedly better" [43]❸ "There was a marked difference between how the two groups dealt with ❸ situations" [36] "There was a marked difference between the groups when dealing with ❸" [21]	"recalled ❶❺ notably better" [39] "Ritalin-type drugs… clearly improve attention and memory… so does donepezil" [35]❶	---

Improvement or "Bettering"	"improved performance" [33]❷ "improves a pilot's performance and skills"[15]❸❹ "can improve the performance" [41] "showed improved… and performance"[44]❶❷ "has been shown to boost the performance" [45]❶ "has been shown to boost the performance" [40] ❶❸ "helped ❹ better and handle ❶❸"[46] "showed Improved performance" [47] ❶ "performed better" [48]; [21]; [36] ❶ "performed better" [34]❶ "performed better"[40] ❶❸ "did better" [49] ❶❸ "did better" [50]❸❹ "were more adept (at extremely)"[47]❶❷ "coped better with the flood of information"[33]	"showed improved memory…" [44]❶❷ "improved the memory of fighter pilots" [16]❺ "could improve the memory of fighter pilots"[14]❶❺ "improves long-term and recent memory and recognition tasks" [44] "Thought to boost memory"[16] "boost for healthy memory"[33] "There is already evidence that even nimble memories can be improved." [11]	"has also been shown to boost the brain function"[48] "also has been found to boost the brain function"[19]; [18] "But Modafinil does not stand alone in its ability to sharpen the mind… donepezil has been shown to… boost performance in tests of cognitive skill"[48] "[these drugs] also have the potential to deliver unexpected psychological benefits to the rest of the population" [36]
Improvement + Diminutive	"may give a boost" [31] "may boost highly skilled performance, where concentration and alertness are prerequisites" [21] "may also boost performance in situations where concentration and alertness are vital" [36] "might increase alertness and concentration to minimize risk of pilot error and maximize endurance"[40], [45] "Both drugs are thought to boost highly skilled performance, where concentration and alertness are prerequisites" [40] "performed slightly better" [34]❶	"showed some improvement in short-term memory"[31] "slightly helped airline pilots retain"[50]❷❺ "may offer more powerful, better targeted and longer lasting improvements in mental acuity" [21] "may well improve memory" [30] "may offer help to older people with benign memory loss"[15] "When confronted with ❸ new transponder codes and a series of air traffic control commands, older pilots who took donepezil… were less likely to forget ❺"[32]	"Drugs already on the market… have been shown in small studies to improve the performance of healthy brains, though not by much."[35]
All report a change in general performance. Some specify changes in: ❶flight simulator; ❷complex task; ❸emergency; ❹landing; or, ❺training or learning. Those highlighted in red are results of the DFSS that have been reported at the "extended" level, while those in black are findings reported at the "specific" level. Statements shown have been truncated. The most common roots are: Donepezil _____; or, Pilots who took donepezil_____ than the control group. If the root is different, more context is given.			

Table 3-4: Statements of the results of the DFSS as reported in bioethics literature. Reported findings are divided by effect on performance, memory, and brain, mind or mental capacity, and are further divided by how those effects are presented. The results presented in M and B were also divided into two levels, specific results (black) and extended results (red).

	Task Performance	Memory	Brain, Mind, Mental Capacity
Enhancement	"did enhance performance "[24] "the two areas of enhanced performance were ❹, and handling ❸, both of which are attention-intensive tasks"[22]	"evidence for enhanced memory encoding and increased retention in normal humans exists"[51] "Research on drugs that may enhance…the retention of complex skills…suggest that the possibilities for biomedical enhancement are likely to grow rapidly in coming years"[52] "the scepticism exhibited by some who argue finding such drugs [`smart drugs` i.e., memory enhancing agents] is impossible is perhaps not warranted"[29]	"Research has also indicated possible venues for cognitive enhancement"[53] "could possibly become enhancers of cognitive performance"[23] "There is associated research into brain-enhancement drugs…which have enhanced the cognitive performance of aircraft pilots"[26] "Prescription medications such as donepezil…are being investigated for their potential to enhance memory, cognition, and executive function in healthy individuals"[5]
Significance	"showed a highly significant increase in performance"[54]❷	"had significantly better post-training retention"[5]❷❸	---
Non Specific	"one intriguing report suggests an effect in the setting of highly skilled performance"[55] "has shown efficacy"[29]	"Attention, memory, and learning can also be modulated in healthy people"[27]	---
Specific	"In the donepezil group, the flight performance on day 30 was found to be similar to performance after initial training, whereas in the placebo group, flight performance declined."[38]*	---	---

Improvement + Superlative	---	---	---
Improvement or "Bettering"	"has been found to improve the performance"[56]❶❷ "performed better"[55]❶❷❸ "performed better"[57]❶❸ "improve normal performance in laboratory vigilance tests"[27] "improves the performance of commercial airline pilots"[23]❶ "improves performance"[58] "improved the subjects' ability to respond to ❶, in-flight ❸"[20] "outperformed a control group on tests of performance"[28] "appeared to improve their performance when compared to those on placebo"[22]	"it improved retention of ❺and episodic (long-term) memory"[24] "was shown to improve retention"[59]❷❺ "were able to better retain information"[53] "can improve memory and executive function"[6] "these drugs may not simply…improve recall. Some of them may also improve executive function"[58]	"has improved cognitive performance"[25] "improve cognition"[58] "there are several drugs that can improve cognitive abilities such as intelligence, concentration, learning, and memory"[28]
Improvement + Diminutive	"may improve normal performance under some circumstances"[57]	---	---

All report a change in general performance. Some specify changes in: ❶ flight simulator; ❷ complex task ; ❸emergency ; ❹ landing; or, ❺ training or learning. Those highlighted in red are results of the DFSS that have been reported at the "extended" level, while those in black are findings reported at the "specific" level. Statements shown have been truncated. The most common roots are: Donepezil _____; or, Pilots who took donepezil_____ than the control group. If the root is different, more context is given.

*Of note, [38] was the only bioethics article that provided a critique of the DFSS.

Qualifying clauses

We also examined the qualifying clauses made in the DFSS and reported by a handful of media and one bioethics article (N=4/27M, 15%; N=1/22B, 5%). The authors of the original study presented both practical and epistemic qualifications. *Practical* qualifications warned of potential side-effects of the drug (in the CE context) and a need for a larger sample size or further tests. These qualifications were each only reported by two media articles. The *epistemic* qualification that "these results should not be interpreted to advocate widespread use of donepezil in nondemented populations" [1]) was reflected in only 11% of media articles (N=3/27). Only one bioethics article reports the second epistemic qualification that "[a]lthough these findings may support interpretations of the effects of cholinergic augmentation on cognitive processing, the precise neurochemical mechanisms of action remain to be fully delineated" [1]).

Reporting of the study characteristics of the DFSS

To establish whether the characteristics of the DFSS (e.g., subject information, sample size (n), study design) were accurately reported in media and bioethics literatures, we directly compared the claims of the primary study to those made in media and bioethics articles (Table 3-5). All media and all but one bioethics article reported at least one study characteristic. Table 3-5 shows the numeric breakdown of media and bioethics article-claims as they correspond to each category and are distributed across the Euler classes. The majority of article-claims made were synonymous (i.e., accurate) with those found in the DFSS ("same" class; Table 3-5).

However, when the categories of study characteristics were analyzed independently, we found two categories that did not reflect this trend: the "subjects" category and the "methods" category. The "subjects" category was also the category that had the largest total number of article-claims (Table 3-5). In addition to finding a high number of article-claims about the "subjects" category in the "same" class, we found a high number in class "IO," the "Some A' are B, some A' are not B" class. In this class, part of the claim might be accurate, or under certain circumstances it may be accurate, but not always. We also found a high number of article-claims in the specifications ("All B are A'") class (Table 3-5).

Table 3-5: Accuracy of study characteristics reported. Media and bioethics articles reported most of the characteristics of the DFSS accurately. The first column gives "A'", the claims made in the study, while the following five columns provide the number of articles that made "B", alternative claims that describe the same study characteristic, in each of five Euler classes (representing varying degrees of accuracy). Absolute numbers represent how many different articles had at least one B description in each sub-category.

LEGEND: Each article was counted only once per sub-category (e.g., nondemented, placebo controlled) of study characteristic even if it made two or more separate claims that fell into that sub-category. This metric is captured by the term "article-claim". Thus, the numbers in each cell refers to the number of "article-claims" made per sub-category added together for each category in each class. To calculate the total # of article-claims made per class, the number of article-claims per category were added together. Theoretically, a single article could account for 15 category claims since they could have made a claim about each sub-category of study characteristics. To calculate the total # of article-claims made per category, the number of article-claims per class were added together. Here, a single article could account for a maximum of 5 times the number of sub-category claims that is possible in each category, since they could have made a claim about each sub-category that fell into each class.

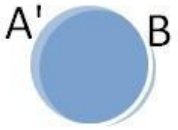
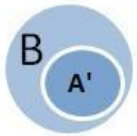
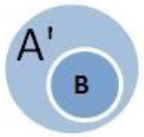
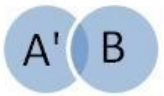
			Class of Proposition											
														
			Same Class (same or synonyms)		**A:** ***All A' are B*** (B is an overstatement, generalization)		**Reverse of A:** ***All B are A'*** (B is a specification)		**IO:** ***Some A' is B, some A' is not B*** (variable)		**E:** ***No A' is B*** (mutually exclusive classes)		**Total # of article-claims per category**	
		Values for A'	*Media (n=27)*	*Bioethics (n=22)*	*Media (n=27)*	*Bioethics (n=22)*	*Media (n=27)*	*Bioethics (n=22)*	*Media (n=27)*	*Bioethics (n=22)*	*Media (n=27)*	*Bioethics (n=22)*	*Media (n=27)*	*Bioethics (n=22)*
Categories of Study Characteristics	**Subjects**	Licenced; Aircraft; Pilots	**11**	**10**	---	---	**14**	**6**	---	---	---	---		
		Nondemented	---	**1**	---	---	---	---	**11**	**12**	---	---	**44**	**37**
		30-70 y.o.; mean 52 y.o.	**5**	**2**	---	**1**	---	---	**3**	**5**	---	**1**		
	n	18	**9**	**2**	**1**	**1**	---	---	---	---	---	---	**10**	**3**
	Design	Placebo Controlled	**14**	**6**	---	---	---	---	**4**	**1**	---	---		
		Double Blind	---	**2**	---	---	---	---	---	---	---	---	**18**	**10**
		Randomized Parallel Group		**1**	---	---	---	---	---	---	---	---		
	Methods	5mg donepezil/day	**3**	**4**	---	---	---	---	---	---	---	---		
		30 days of treatment between test days (2 days)	**3**	**1**	---	---	---	---	**5**	**5**	---	**2**	**22**	**14**
		7, 75 min. tests at baseline	---	---	---	---	---	---	**4**	---	---	---		
		2 tests post 30 days	**1**	**1**	---	---	---	---	**6**	**1**	---	---		
	Test	Flight simulator; simulation	**19**	**12**	**1**	**3**	**1**	---	---	---	---	**1**	**21**	**16**
	Tasks Performed	"a complex series of Air traffic Control instructions"; "the flight tasks (...) are more difficult than (...) routine"	**6**	**6**	**6**	---	---	---	**3**	---	---	---	**27**	**12**
		Emergencies	**10**	**5**	---	---	---	---	---	---	---	---		
		Landing	**1**	**1**	---	---	**1**	---	---	---	---	---		
		Total # of article-claims per class	**82**	**54**	**8**	**5**	**16**	**6**	**36**	**24**	---	**4**		
		# of articles contributing to this total	**25**	**16**	**7**	**5**	**15**	**6**	**22**	**14**	---	**4**		

Figure 3-1 presents a visualization of the distribution of claims made in the "subjects" category, showing how claims can represent the same characteristic category yet fall into different proposition classes. This figure also demonstrates the range of qualitative differences possible in the translation of discrete categories of information.

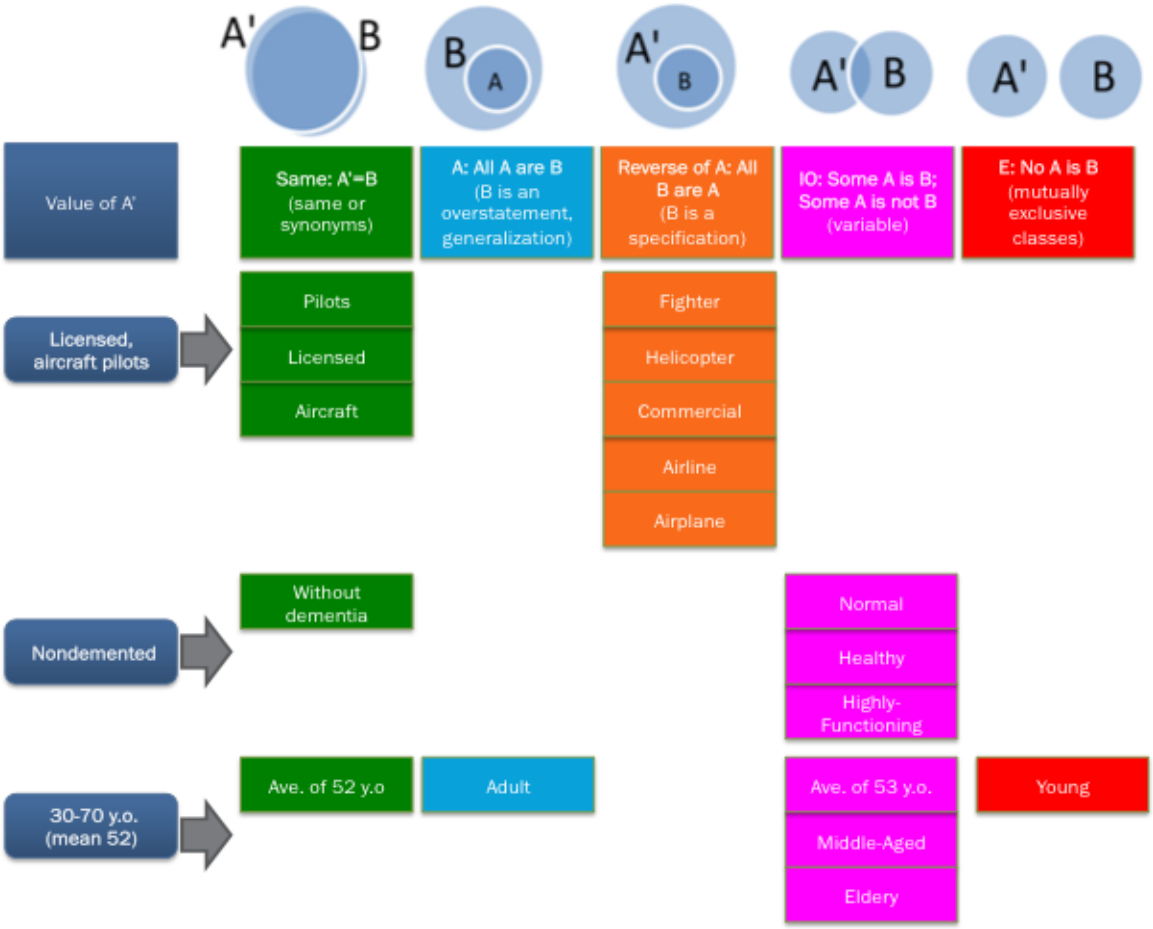


Figure 3-1: A visualization of the characteristics of the "subjects" category (from Table 6) as stated in the DFSS (A') and their translation into media and bioethics article-claims (B). This study category represented the largest total number of article-claims and its article-claims were distributed across the various classes.

Limitations

In spite of broad searches and the use of multiple databases, our sample may not be exhaustive of all articles on non-medical use of donepezil with reference to the DFSS. The small sample size also makes it difficult to make any wide-reaching conclusions. Like other qualitative content and discourses analyses, though coding was double-

checked and thoroughly pilot tested, controlling for subjectivity of data gathering and analysis is challenging and may represent another study limitation. Further, our findings should not be interpreted as an accusation of the authors of the DFSS or of the specific journalists or scholars who were authors of the media and bioethics articles. We understand that the reported media statements reflect an amalgamation of data and opinions and do not necessarily reflect the opinions of the authors. Accordingly, the content of our sample should be viewed as a reflection of what members of the public have access to, rather than the individual voice of the author *per se,* and our findings should be viewed as a detailed exploration of the challenges of interpreting complex data and their contribution to contemporary ethics debates about neurological advances in healthcare and beyond.

Discussion

This study examined media and bioethics coverage of the DFSS, which has served as a landmark paper in the CE debate. We specifically focused on how the DFSS is reported in media and bioethics articles that engage in the debate in order to characterize how this discussion contributes to the claim that donepezil has CE effects.

Our key findings demonstrate that both media and bioethics articles convey high expectations of pharmaceuticals that have been associated with CE. These expectations are epitomized in the headlines and titles of articles that engage in the CE debate, as well as in the colloquialisms that are used to explicitly refer to donepezil within a discussion of CE (Table 3-1). Emphasis is placed on the possibility that donepezil could affect cognition or intellectual capacity while consistent use of enhancement language implies that this effect is a desirable or laudable goal. This supports the previous findings of two authors of this study (CF and ER) who found that media and bioethics discourses were generally enthusiastic in portraying CE effects of methylphenidate on cognition [10]. However, we did see a difference between headline and title references to pharmaceutical use as well as to the potential medical use of donepezil (i.e., for memory restoration). While media headlines reference both topics, bioethics titles focus on enhancement and reflect coverage of general issues related to the CE debate. This indicates that donepezil

is rarely examined in the bioethics literature as a cognitive enhancer in its own right, but has become part of the larger debate on CE where it is taken to be an illustrative example.

Our analysis of how the results of the DFSS are depicted in media and bioethics articles provides further confirmation of the high expectations for CE that we found in headlines, titles and colloquialisms. Hype of a CE effect occurs both within and across individual articles as the findings of the DFSS are consistently presented at two levels (i.e., specific or extended; Tables 3-3 and 3-4).

In both literatures, an enhancement effect is reported with reference to three broad categories of characteristics, namely, task performance, memory, and brain, mind, or mental capacity. The way this effect is conveyed, either through improvement or explicit enhancement language, and what category of characteristic is emphasized changes depending on the level at which the result is reported. Generally, media and bioethics articles follow the same result reporting trends.

We found a clear trend to use explicit CE language (e.g., "enhance") and to report effects on memory and brain, mind, and mental capacity when articles report the findings as *extended* results. This trend is particularly salient in bioethics articles, where the majority of result claims use enhancement language at this level. The proportion of result claims made by the media that use enhancement language does increase at the extended level; however, the majority of claims use "improvement" language. When improvement language is used at this level, both literatures equally make reference to all three categories of performance improvement. Conversely, when reporting results at the *specific* level, both literatures use a higher proportion of improvement rather than explicit enhancement language. Both literatures overwhelmingly report an improvement in task performance, followed by an improvement in memory. An improvement in brain function is only raised as a *specific* result of the study by bioethics articles. Too few articles use enhancement language at this level to establish any trend.

Specific reports of improvements in performance and (memory to a lesser degree) are often associated with discrete tasks, such as flying a flight simulator or performing an emergency procedure. However, further specification of what aspects of these broad characteristics are influenced by donepezil is rare (i.e., executive function, short or long-term memory) as is a precise description of the original level of significance of the

findings or what trend contributed to this significant difference (i.e., a decrease in the performance of the pilots in the placebo group). Evidently, the findings of the DFSS that are reported, as well as the level of detail conveyed, change substantially as they are reported at the specific and extended levels. The direction of this change towards more enhancement language and a greater focus on cognitive traits as reports move away from a focused discussion of the DFSS supports the perception that the results of this study have been hyped and inappropriately taken into the CE context. Further, we found that only a handful of media articles and one bioethics article acknowledge the qualifying clauses made in the DFSS.

Our final investigation of how accurately media and bioethics articles translate and present the characteristics of the DFSS (e.g., subjects, study design) showed that overall most study characteristics are accurately identified; only a few are clearly incorrect (Table 3-5). However, we found high levels of variability in claims related to the "subjects" and "methods" categories. The information provided on the subjects category is straightforward in the DFSS, so these discrepancies stand out. There is a trend to report subject characteristics using the language of the CE debate, e.g., "healthy," or in relation to the expectation that the drug may be useful for "fighter" or "commercial" pilots (Figure 3-1). Close examination of the DFSS itself shows that information on the methods used is ambiguous and difficult to interpret, making accurate restatement of these characteristics legitimately difficult. Such variable accuracy in the reporting of study characteristics, combined with our findings related to the reporting of the study's results, suggests that the high expectations for CE associated with donepezil use cannot be accounted for by simple inaccuracy in reporting of the primary paper. More complex interactions seem to be governing the accurate dissemination and interpretation of the findings of the study.

We explore the potential factors involved in the portrayal of the results of the DFSS and their implications for the translation of complex neuroscience research in the following discussion points: 1) the magnification of ambiguity in the CE debate; and, 2) the need to build social awareness into neurological training given expectations for CE drugs.

The magnification of ambiguity

Further comparison of the results of the DFSS that were reported in media and bioethics articles with the conclusions drawn by the authors of the study in its "discussion" section provides insight into how ambiguous claims are magnified in the dissemination of knowledge.

The findings presented by the DFSS in its "abstract" or "results" section (Table 3-2) do not claim an improvement in performance (indeed no mention of an "improvement" is made until the discussion). Interestingly, however, we found that the majority of *specific* results reported by both media and bioethics articles conveyed the general result that: "donepezil improved the performance of pilots" (Tables 3-3 and 3-4). This interpretation seems to have been confounded with the DFSS' claim that: "the donepezil group showed greater ability to retain the capacity to perform" [1] (Table 3-2, abstract). Although a slight change of interpretation, it is significant: the level of performance did not increase, rather the ability to perform at the same level again increased.

The relevance of this change in interpretation for the enhancement debate, where improvement above an individual's norm is the goal, is made clear when the results of the DFSS are compared against those of similar studies on the effects of acetylcholinesterase inhibitors: there is limited evidence to suggest that even the effect reported by the DFSS exists. A recent review concluded that the available data on donepezil does not allow any firm conclusions to be drawn; and specifically, that the DFSS only demonstrates that donepezil "*might* improve the retention of training on complex aviation tasks" ([7]; emphasis added). An additional study that reviewed the level of evidence provided by the DFSS and other studies on acetylcholinesterase inhibitors also concluded: "the available evidence does not appear to support the widely cited conclusion that donepezil improves the retention of training" [38].

However, in the discussion of the DFSS the authors do raise the idea of an improvement and relate it to cognitive performance. They present the qualifying clause: "these results should not be interpreted to advocate widespread use of donepezil in nondemented populations" [1] before stating that "[n]onetheless" [1], their results are consistent with those of previous studies, which "have reported that cholinesterase inhibitors improve cognitive performance" [1]. In this way, despite this and other

qualifications, the authors make a clear connection between the findings of their study and a CE effect. Moreover, the authors go on to dedicate the final paragraph of their discussion to raising concerns about CE, directly raising and naming the concept of CE for the first time.

Thus, the *specific* results reported in media and bioethics articles seem to be attributable, at least in part, to ambiguity imparted by the authors in the original publication as they attempted to connect their findings to those of other studies and to the CE debate. This also appears to account for the increase in explicit enhancement claims focusing on intelligence and memory factors that we found when results were reported at the *extended* level. Indeed, the authors later clarified the limited support their study provides for the use of donepezil for CE in a response to a commentary that cast doubt on this connection: "our results should not be interpreted as a recommendation for the use of donepezil as a drug to improve flight performance" [60]; however, this statement does not prohibit the interpretation that donepezil *could* improve flight performance, or dispel the previously drawn connection to CE in general.

Problems created in the dissemination of research results emerging from discrepancies within one primary study are certainly not unique to the CE debate or the study we examined. For example, a study on the dissemination of ADHD research (primary studies that associate polymorphisms of a specific gene with ADHD) found: (1) internal inconsistencies between claims made in the results and those presented in the conclusions; (2) a strong conclusion claim in the summary, while data that limit this conclusion were only present in the results section; (3) the inappropriate extrapolation of findings to therapeutic prospects [61]. These data offer support for our finding of a discrepancy between the data reported in the results section of the DFSS and the generalized conclusion offered in the study's discussion. Previous research on developments in biotechnology, including neurotechnology, has also shown that the majority of authors include both a qualifying clause in their paper, that addresses the uncertainty inherent in their data, as well as a main explanation of their data, that is designed to provoke discussion with their peers. Yet, often only the main explanation is widely disseminated in print media [62, 63]. Further, the explanations that were reported in the media have been found to be inconsistent with what was actually reported in the

study, reflecting "different versions of future relevance" [62] as the data is interpreted and translated. This phenomenon provides greater insight into our finding that media and bioethics articles reported more generalized conclusions than qualifying clauses and helps to account for the further discrepancy observed in the facts reported by media and bioethics articles.

Authors of secondary literature such as media and bioethics articles have the challenge of deriving the meaning of general explanations put forward by primary authors in order to reiterate that meaning in their articles. As the explanations of findings provided in studies are not always clearly or consistently portrayed throughout a paper, their interpretations are not always successful. The presence of expectations in a field of study has also been found to influence the claims made by authors of both primary and secondary literature [62]. Awareness of the challenge of deriving meaning from study results in the face of potentially misleading primary explanations and pervasive expectations provides insight into how we can best mediate the negative effects of such situations.

Expectations, values and so-called, "cognitive enhancement drugs": Building social awareness skills in neurology

The role of expectations (individual or social) in the dissemination of knowledge related to biotechnology has been well charted. As Brown describes, anticipation of a prospective future is crucial for project development, funding, and creativity [62]. Yet, hype around expectations can threaten the legitimacy of a project. Unfortunately, the perpetuation of expectations rarely occurs without hype. Where there are expectations, a spatial dynamic is often created "whereby the further we travel from the source of knowledge production, the more colourful and flamboyant become the promissory properties of knowledge" [62]. This trend is consonant with previous work done by one author of this study (ER; [9]). Our current data also demonstrate this spatial dynamic. Starting with the primary authors' description of their findings in the results section and moving first to the descriptions found in their discussion, we begin to see this trend. Then as we explore the different claims made in media and bioethics articles as they presented the results of the DFSS on two levels (*specific* and *extended*), the trend is clearer. Finally,

when we consider the high expectations for CE found in our colloquialism and headline data it is apparent that there is a distinct trend to elaborate on findings, integrating expectations rather than uncertainty, as claims are further removed from the source of the data. As a public, we become mutually enrolled in this spatial dynamic of expectations. Researchers, patient organizations, and policy makers all become invested in the promised future and are thereby: "left with few contextual resources with which to judge the veracity of promissory claims. Spatial remoteness "drives a wedge between the privately cautious world of bench science and wider constituencies within the knowledge economy of expectations" [62]. Unchecked expectations can lead to a general confounding of the objectivity and legitimacy of scientific data, limiting the ability of an interested public to ascertain the implications of new research.

Additionally, the discrete terms used to frame the data to suit perceived expectations may have powerful implications for clinicians, patients, and the public. For example, in a study examining the psychology driving the demand for cognitive enhancement Riis *et al.*[28] found that study participants were more reluctant to use drugs to enhance targeted traits they identified as "fundamental" to their self-identity. Kindness and social comfort were ranked as more fundamental than traits like foreign language ability and concentration. Our analysis demonstrates that more often than not, media and bioethics article descriptions of the effects of donepezil were broad, rather than specific (see Tables 3-1, 3-3 and 3-4 for examples). These loose descriptions may confound individuals' ability to connect these drugs to traits they feel are fundamental to their self-identity. Further, Riis *et al.* [28] found that when the effects of the drugs were framed differently, i.e., as "enabling" rather than as "enhancing", study participants' willingness to use the drug to change a fundamental trait increased (significantly). A similar phenomenon was noted in a study on the media portrayal of methylphenidate as a CE agent. Sensational terms and analogies used to describe the drug as a CE agent influenced stakeholder understandings of drug efficacy [10, 64]. While our study did not examine the framing of drug effects on individual understanding, our data demonstrate that both media and bioethics articles report the effects of drugs in several different ways, often in the same article (i.e., in headlines, titles and colloquialisms as well as at the different levels of results reporting) and in line with expectations for a CE effect rather

than following canons of scientific evidence and rigor. This influence of expectations on the presentation of drug effects in media and bioethics articles may also confound an individual's perception of whether they would be comfortable changing a specific trait. If the expectations involved in framing this critical debate subsequently impact consumer interest and acceptability of pharmaceutical products, such messages could have important outcomes for individual patients and society at large.

The influence of expectations on the presentation of drug effects may also reflect the influence of social pressure on the debate over CE. It has been widely recognized that one of the risks of endorsing the use of pharmaceuticals for enhancement purposes is that it may perpetuate social pressures, such as the pressure to perform, be productive, highly intelligent, or competitive [65]. Unchecked, hype of expectations influenced by social pressure may perpetuate social values that are not in line with the interests of the population as a whole, or do not reflect the interests of all types of individuals [66]. These performance-oriented values, though viewed by some as integral to a thriving society (e.g., [67]), may negatively impact individuals' ideas of their own self-worth, fostering anxiety and discontent with gifts that have been acquired through genuinely lived experiences [65], and subsequently inducing a society that instead celebrates the abilities of the most common denominator, or those traits that are the most in line with quantifiable economic and military principles of productivity. The long-term social consequences of drug use for CE purposes are unknown; however, the risk of inducing a "medicated normality" [68], has been raised, where a loss of cultural and social diversity, accompanied by intolerance towards difference, would manifest as an assault on the autonomy of individuals [68]. Others have raised the possibility that such drug use could induce unanticipated changes to the complex biosocial and psychological functions of the brain, altering our social behaviour in an altogether different way [69]. The potential risks of unmediated social pressure interacting with individual use of drugs for CE purposes should not be overlooked.

Recent research on the role of social pressure has isolated a "funnel phenomenon," [70] where social pressure covertly drives individual choice in the use of methylphenidate among students for CE [70]. When prompted, stakeholders in the debate (e.g., students, health care providers) firmly believed that students' personal values

guided their decision to use methylphenidate (i.e., students acted autonomously). However, they also believed that social pressure to perform was so strong in the academic community that it created "a form of social determinism leading to conformity with social values through a concession of personal values" [70]. The authors concluded that personal values are an ornamental, rather than substantial, factor in decision making. This finding has substantial implications. If health care professionals believe individuals are making autonomous choices, yet external pressures are implicitly shaping these decisions, the task of determining whether an individual is being coerced to change a trait (whether they consider it to be fundamental or not) becomes virtually impossible.

It has been recognized that as requests for "neuroenhancements" enter the clinical realm, physicians will be left with the difficult task of understanding this "framing problem" and presenting it to their patients to determine if their patient is genuinely interested in these medications and has a solid understanding of their associated harms (i.e., side-effects or risk of changing fundamental traits). However, recently published guidelines on how neurologists should deal with these requests [6] concluded that neurologists were sufficiently aware of these social factors and thus left out specific recommendations on how to take social pressures into account, opting instead to support a physician-patient discussion [71]. As demonstrated by the previous data, there is a risk that within the context of the patient-physician relationship it will be difficult to determine whether the individual is in fact making autonomous decisions. Further, in absence of its presence in the guidelines, the presumed importance of this issue may be overlooked. An extended patient-physician discussion may uncover reasons for the request, however, without specific guidelines to address social pressure in the clinical context, physicians may consider further attention to these issues unnecessary. Research in other decision-making contexts (e.g., end-of life decision-making) has shown that clinicians, including neurologists, often assume they act objectively in the face of persistent social norms [72]. However, there is evidence that social context and specific physician characteristics such as practice setting, specialty, religion, gender, and age can shape decision-making [73-75]. The need to explicitly acknowledge and tackle social factors could be more widespread and pervasive.

It has been suggested that the description of the lack of data on the safety and efficacy of cognitive enhancers would deter physicians from prescribing them [71]. However, as our study shows, this dearth of scientific evidence can be difficult to comprehend due to hyping of the results in media and bioethics literature. Indeed, these very guidelines cited the DFSS as evidence in support of the efficacy of these drugs, rather than as an example of the lack of evidence available [6]. Clearly, there is an important interaction between the presence of social pressure, the existence of expectations for CE, and the ability to adequately disseminate information on safety and efficacy. We must exercise precaution and attempt to explicitly account for both social pressure and safety and efficacy as we continue to discuss the use of drugs for CE.

Evidently, educating the public on the level of evidence informing the CE debate and safeguarding consumers from the potential harms of using drugs for CE is fraught with difficulty. As stated by Brown, it is "difficult to police the boundaries between the uncertainties of scientific research values and the certainties of news reportage" [62], especially in the context of CE where high expectations pre-exist evidence. However, the players involved in generating media reports, bioethics articles, policies related to developments in biotechnology, systemic reviews of areas of study, and fielding individual requests for these drugs are of crucial importance for the primary reason that patient, or consumer, interest will be impacted. This points to the importance of curated public information and support for relevant initiatives at the level of clinical care and health policy.

Strengthening the community review process and building awareness of social factors into clinical consults

Strengthening the review process such that the findings of a group of individual studies that cover one area, or class of drug, would be analyzed and summarized for wide public dissemination once a viable level of evidence has been reached is one option for tackling the issue of limited efficacy. Independent parties (such as that formed by Repantis et al. [7, 76, 77]) or interdisciplinary panels of relevant experts could fulfill this mandate as suggested in other contentious areas of neurology [78, 79]. Clinical journals like *Neurology* and *JAMA* have started to publish similar-minded "patient pages," which serve

a similar goal for health information and treatments. This could be extended to the trickier context of reporting research results to avoid over-generalization of or disproportionately heralding the findings of small studies conducted on homogeneous populations as offering support for broad expectations of health benefits or non-health benefits like enhancement. Such frameworks could help the public mitigate the harms of misinformation on issues such as safety and efficacy, as well as the yo-yo effect of hope and disappointment that often accompanies news coverage of clinical trials for highly anticipated treatments [62]. These reviews could also be useful to experts in other fields like bioethics and policy-makers who need to use neurological knowledge to discuss and comment on ethical aspects of medicine. Independent networks are beginning to form specific knowledge translation platforms for the purpose of distributing synthesized information to stakeholders (e.g., Neurodevnet [80]). Other public neuroeducation initiatives are also underway, such as public education outreach programs and an initiative to develop neuroscience communication experts [81].

Mitigating the social pressure that may be impacting expectations of CE, reporting of drug effects for CE purposes, and consumer interest in CE, will be an ongoing process. Organizations have begun developing explicit recommendations on how to deal with social pressures surrounding CE agents [68]; however, more work is needed in this area, especially with specific attention to the clinical context and individual consults. Research has also provided insight into how neurologists can integrate knowledge of social factors and circumstances that shape their decision making as well as emerging research at the interface of neuroscience and the social sciences, e.g., social neuroscience, into their daily practice [72]. As the CE debate continues, caution should be further applied to avoid complicity with negative social norms that surround intellectual disability. There is a need to move beyond issues of safety and efficacy to consider the type of society we live in today. We need openly question these expectations and desires to ensure that an interest in progress does not come at the cost of a balanced life-style or the possibility of different ways of being; or, potentially more dangerous, does not oppress or devalue different lives. Attention to disability rights literature may help bioethicists and clinicians become acquainted with the obligations we have to support these populations.

Conclusion

Our findings support the more general claim that both media and academic literature often misrepresent the limited conclusions that can be drawn from basic research, putting them in line with expectations that may be heavily influenced by prominent social pressures. A complex interaction between the authors of primary and secondary literature, and widespread expectations and social pressures, may contribute to this phenomenon. Mediation of such an interaction will require a concerted effort to develop translation programs to evaluate and appropriately disseminate the knowledge produced by individual studies within a field of research, as well as to introduce strategies to address social pressure at the level of clinical care. Failure to do so may preclude the reliable interpretation and dissemination of neuroscience research, with potentially grave implications for patients and consumers as they attempt to evaluate the veracity of claims and make informed decisions.

References

1. Yesavage, J.A., et al., *Donepezil and flight simulator performance: Effects on retention of complex skills.* Neurol, 2002. **59**(1): p. 123-125.
2. Greely, H., et al., *Towards responsible use of cognitive-enhancing drugs by the healthy.* Nature, 2008. **456**(7223): p. 702-5.
3. Singh, I. and K.J. Kelleher, *Neuroenhancement in young people: Proposal for research, policy, and clinical management.* AJOB Neurosci, 2010. **1**(1): p. 3-16.
4. Appel, J.M., *When the boss turns pusher: a proposal for employee protections in the age of cosmetic neurology.* J Med Ethics, 2008. **34**(8): p. 616-8.
5. Warren, O.J., et al., *The neurocognitive enhancement of surgeons: An ethical perspective.* J Surg Res, 2009. **152**(1): p. 167-172.
6. Larriviere, D., et al., *Responding to requests from adult patients for neuroenhancements: Guidance of the Ethics, Law and Humanities Committee.* Neurol, 2009. **73**(17): p. 1406-12.
7. Repantis, D., O. Laisney, and I. Heuser, *Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: A systematic review.* Pharmacol Res, 2010. **61**(6): p. 473-81.
8. Racine, E., O. Bar-Ilan, and J. Illes, *Brain imaging: A decade of coverage in the print media.* Sci Commun, 2006. **28**(1): p. 122-142.
9. Racine, E., D. DuRousseau, and J. Illes, *From the bench to headlines: Ethical issues in performance-enhancing technologies.* Technol, 2007. **11**: p. 37-54.
10. Forlini, C. and E. Racine, *Disagreements with implications: Diverging discourses on the ethics of non-medical use of methylphenidate for performance enhancement.* BMC Med Eth, 2009. **10**: p. 9.
11. Arnst, C., *"I can't remember"; Drugs to stave off age-induced memory impairment may be on the horizon*, in *Business Week.* 2003.
12. Shin, S.-J. and O. Lemon, *Diagrams*, in *The Stanford Encyclopedia of Philosophy (Winter 2008 Edition)*, E.N. Zalta, Editor. 2008.
13. Copi, I.M., *Introduction to logic.*1982, New York: Macmillan.
14. Morgan, J., *Brain-boosting drugs could soon become the smart choice*, in *The Herald Final.* 2008.
15. Stuttaford, T., *Memory drug has landed-Medical briefing*, in *The Times.*2002.
16. Burne, J., *Can taking a pill make you brainy?*, in *Daily Mail.* 2007.
17. Farah, M.J., et al., *Neurocognitive enhancement: What can we do and what should we do?* Nat Rev Neurosci, 2004. **5**(5): p. 421-5.
18. Healy, M., *Newest drugs act as brain's fountain of youth*, in *The Grand Rapids Press.* 2005.
19. Healy, M., *Call these drugs IQ-profen: Brain research is leading to quick advances toward 'smart pills'*, in *Los Angeles Times.* 2005.
20. Mehlman, M.J. and J.W. Berg, *Human subjects protections in biomedical enhancement research: Assessing risk and benefit and obtaining informed consent.* The J Law Med Ethics, 2008. **36**(3): p. 546-9.
21. Laurence, J., *Messing with our minds*, in *The Independent.* 2005.
22. Whitehouse, P.J., *Paying attention to acetylcholine: The key to wisdom and quality of life?* Acetylcholine in the Cerebral Cortex, 2004. **145**: p. 311-317.
23. Racine, E. and J. Illes, *Neuroethical responsibilities.* Can JNeurol Sci, 2006. **33**(3): p. 269-77, 260-8.
24. Bolt, L.L., *True to oneself? Broad and narrow ideas on authenticity in the enhancement debate.* Theor Med Bioeth, 2007. **28**(4): p. 285-300.
25. Lanni, C., et al., *Cognition enhancers between treating and doping the mind.* Pharmacol Res, 2008. **57**(3): p. 196-213.
26. Vincent, J.A., *Science and imagery in the 'war on old age'.* Ageing Soc, 2007. **27**: p. 941-961.
27. Chatterjee, A., *Cosmetic neurology and cosmetic surgery: Parallels, predictions, and challenges.* Camb Q Healthc Ethics, 2007. **16**(2): p. 129-37.
28. Riis, J., J.P. Simmons, and G.P. Goodwin, *Preferences for enhancement pharmaceuticals: The reluctance to enhance fundamental traits.* J Consum Res, 2008. **35**(3): p. 495-508.
29. Gerlai, R., *Memory enhancement: The progress and our fears.* Genes Brain Behav, 2003. **2**(4): p. 187-190.

30. Reucroft, S. and J. Swain, *Smart drug*, in *The Boston Globe.* 2002.
31. Gibson, E., *Mental pick-me-ups: "Cognition drugs" such as Adderall and Provigil are fast gaining popularity--despite health and ethics issues*, in *Business Week.* 2008.
32. Evenson, B., *Alzheimer's drug improves 'working memory': Side effects possible: Older pilots remember training better in test*, in *National Post.* 2002.
33. Balfour, N., *Superbrain future, recycled water, better oxygen supply, Alzheimer drug boost for healthy memory*, in *The Sunday.* 2002.
34. McCook, A., *Alzheimer's drug ups memory in healthy pilots*, in *Reuters Health E-Line.* 2002.
35. Kher, U., *Can you find concentration in a bottle?*, in *Time (Canadian Edition).* 2006.
36. *A clever idea? The drugs that made you smart*, in *Irish Independent.* 2005.
37. *NEW Memory pill- In brief*, in *The Times.* 2002.
38. de Jongh, R., et al., *Botox for the brain: Enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories.* Neurosci Biobehav Rev, 2008. **32**(4): p. 760-776.
39. Miller, H. and D. Longtin, *Smart pill, anyone?*, in *The Washington Times.* 2004.
40. Laurence, J., *Mind-enhancing drugs: Are they a no-brainer?*, in *The Independent.* 2009.
41. *Drug found to improve performance among pilots*, in *Airline Industry Information.* 2002.
42. Begley, S., *New ethical minefield: Drugs to boost memory and sharpen attention*, in *The Wall Street Journal.* 2004.
43. Macintyre, B., *Extreme makeover for the brain*, in *The Times.* 2004.
44. *New potential for Alzheimer's and cholesterolemia markets*, in *Medical Marketing & Media.* 2002.
45. *A stimulating debate*, in *Irish Independent.* 2009.
46. Jaffe, S., *Scientists test theories on aging and their resolve: Researchers become case studies for their own work*, in *The Plain Dealer.* 2002.
47. *Briefs: New clues in Alzheimer's,*in *The Record.* 2002.
48. Bee, P., *Smart drugs for straight A's*, in *The Times.* 2007.
49. Rosenthal, R., *Data needed on cognition-enhancing drugs*, in *Pediatric News.* 2009.
50. O'Neil, J., *Testing medicine and memory*, in *The New York Times.* 2002.
51. Choudhury, S., S.K. Nagel, and J. Slaby, *Critical neuroscience: Linking neuroscience and society through critical practice.* Biosocieties, 2009. **4**(1): p. 61-77.
52. Douglas, T., *Moral enhancement.* J Appl Philos, 2008. **25**(3): p. 228-245.
53. Forlini, C., *Examining discourses on the ethics and public understanding of cognitive enhancement with methylphenidate*, in *Programmes de bioéthique, Département de médecine social et préventive, Faculté de médecine* 2008, Université de Montréal: Montreal.
54. Normann, C. and M. Berger, *Neuroenhancement: Status quo and perspectives.* Eur Arch Psychiatry Neurol Sci, 2008. **258 Suppl 5**: p. 110-4.
55. Chatterjee, A., *Cosmetic neurology: The controversy over enhancing movement, mentation, and mood.* Neurol, 2004. **63**(6): p. 968-74.
56. Bush, S.S., *Neurocognitive enhancement: Ethical considerations for an emerging subspecialty.* Appl neuropsychol, 2006. **13**(2): p. 125-36.
57. Chatterjee, A., *The promise and predicament of cosmetic neurology.* J Med Ethics, 2006. **32**(2): p. 110-3.
58. Mehlman, M.J., *Cognition-enhancing drugs.* Milbank Q, 2004. **82**(3): p. 483-506.
59. Cheshire, W., *The pharmacologically enhanced physician.* Am Med Assoc J Ethics, 2008. **10**(9): p. 594-598.
60. Connemann, B.J., et al., *Donepezil and flight simulator performance: Effects on retention of complex skills.* Neurol, 2003. **61**(5): p. 721-22.
61. Gonon, F., E. Bezard, and T. Boraud, *Misrepresentation of neuroscience data might give rise to misleading conclusions in the media: the case of attention deficit hyperactivity disorder.* PLoS One, 2011. **6**(1): p. e14618.
62. Brown, N., *Hope against hype - accountability in biopasts, presents and futures.* SciStud, 2003. **16**(2): p. 3-21.
63. Racine, E. and Z.C.-v. Aesch, *Neuroscience's impact on our self-identity: Perspectives from ethics and public understanding*, in *Neurocultures: Glimpses into an expanding universe*, F. Ortega, Editor, 2011, Oxford: New York. p. 83-98.

64. Forlini, C. and E. Racine, *Stakeholder perspectives and reactions to "academic" cognitive enhancement: Unsuspected meaning of ambivalence and analogies.* Public Underst Sci, 2010. December 5: p. 1-20.
65. President's Council on Bioethics, *Beyond therapy*, 2003, President's Council on Bioethics/Harper Collins: Washington, DC. p. 328.
66. Racine, E. and C. Forlini, *Expectations regarding cognitive enhancement create substantial challenges.* J Med Ethics, 2009. **35**(8): p. 469-70.
67. Sandberg, A. and N. Bostrom, *Converging cognitive enhancements.* Ann N Y Acad Sci, 2006. **1093**: p. 201-27.
68. Committee, W., *Position statement: Psychotropic drugs and expanded uses: An ethical perspective*, 2009, Gouvernement du Quebec.
69. Racine, E. and C. Forlini, *Responding to requests from adult patients for neuroenhancements: Guidance of the Ethics, Law and Humanities Committee.* Neurol, 2010. **74**(19): p. 1555-6; author reply 1556.
70. Forlini, C. and E. Racine, *Autonomy and coercion in academic "cognitive enhancement" using Methylphenidate: Perspectives of a pragmatic study of key stakeholders.* Neuroethics, 2009. **2**(3): p. 163-177.
71. Larriviere, D., et al., *Responding to requests from adult patients for neuroenhancements: Guidance of the Ethics, Law and Humanities Committee Reply.* Neurol, 2010. **74**(19): p. 1556-1556.
72. Racine, E., et al., *Profiles of neurological outcome prediction among intensivists.* Neurocrit Care, 2009. **11**(3): p. 345-352.
73. Rocker, G., et al., *Clinician predictions of intensive care unit mortality.* Crit Care Med, 2004. **32**(5): p. 1149-54.
74. Marcin, J.P., et al., *Prognostication and certainty in the pediatric intensive care unit.* Pediatrics, 1999. **104**(4 Pt 1): p. 868-73.
75. Rebagliato, M., et al., *Neonatal end-of-life decision making: Physicians' attitudes and relationship with self-reported practices in 10 European countries.*JAMA, 2000. **284**(19): p. 2451-9.
76. Repantis, D., et al., *Antidepressants for neuroenhancement in healthy individuals: A systematic review.* Poiesis Prax, 2008. Published online: 27 November 2008.
77. Repantis, D., et al., *Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review.* Pharmacol Res, 2010. **62**(3): p. 187-206.
78. Fins, J.J., et al., *Neuroimaging and disorders of consciousness: Envisioning an ethical research agenda.* Am J Bioeth, 2008. **8**(9): p. 3-12.
79. Racine, E. and E. Bell, *Clinical and public translation of neuroimaging research in disorders of consciousness challenges current diagnostic and public understanding paradigms.*Am J Bioeth, 2008. **8**(9): p. 13-5.
80. Neurodevnet. *Knowledge translation*. Neurodevnet 2010-2011 [cited 2011 June 12, 2011]; Available from: http://www.neurodevnet.ca/kt.
81. Illes, J., et al., *Neurotalk: Improving the communication of neuroscience research.* Nat RevNeurosci, 2010. **11**(1): p. 61-9.

CHAPTER 4 GENERAL DISCUSSION

This thesis has characterized how media and bioethics literature has shaped the discourse of donepezil as a CE agent. By focusing on the case study of how the DFSS was translated in media and bioethics articles we have provided a unique glimpse into the dissemination of science in both public and academic spheres, offering more widely applicable insight into how evidence from neurological research can be taken up in other literatures with important ethics, policy and clinical ramifications. More specifically, we have underscored the hype and complexity surrounding the specific discussion of CE with pharmaceuticals.

We have demonstrated that far from being a simple case of inaccurate representation of scientific studies by the media and bioethicists, the reporting of the DFSS brings forth broad issues relating to the communication of scientific research and bioethics debates. There appears to be a complex dynamic of expectations, hype, and social pressure explaining the apparent discrepancy between, on the one hand, media and bioethics articles presentation of the DFSS and, on the other, what the scientific study merits.

High expectations for a CE effect, which imply a collective desire for enhancement, were reflected in the blatant hype present in headlines, titles, and colloquialisms when media and bioethics articles discussed donepezil as a possible CE agent. When articles discussed the study's results on a general level (i.e., the *extended* level, misrepresentation of the results of the DFSS in line with a CE effect—usually reported as an increase in overall cognition or intelligence—was also present in both discourses. The misrepresentation found within media and bioethics articles was also found in the primary study, as the authors of the DFSS extended their findings to CE applications in their discussion. Permeation of the CE debate within the results of the primary study further exemplifies the assumed value of CE for the individual and for society.

Our analysis of the level of accuracy associated with the reporting of discrete study characteristics also demonstrated that while both media and bioethics articles were generally accurate in their portrayal of most study characteristics, they had difficulty navigating those related to the complex treatment-enhancement distinction. The DFSS was conducted on a nondemented, middle-aged population, recognized by the pilot

industry as having "age-associated" cognitive limitations. Nonetheless both literatures widely interpreted the study as being conducted on "healthy" individuals, whose use of donepezil would fall into the "enhancement" category. As outlined in Chapter 1, aging has been medicalized to a great degree, often being considered as a progressive disease, and the way aging is portrayed in the DFSS seems to support that view. Thus, the results of this study may have been justifiably applied to a discussion of how donepezil may be an effective treatment of aging, counteracting its effects, rather than promoted as a clear-cut CE agent. Since medicalization is highly contingent on social factors, the application of enhancement language to this scenario is not necessarily wrong; rather, it may point to a wider limitation of the treatment-enhancement distinction; specifically, to the need to pay closer attention to the social context within which the application of the desire to increase cognition is being made.

Our results show that in the absence of solid scientific evidence demonstrating that donepezil has an enhancement effect on overall cognition (as reviewed in Chapter 1), donepezil has come to be seen as a CE agent, further reinforcing the idea that drugs that increase intellect are a widespread and laudable goal. Yet, determining whose desire this is and why such messages have been generated remain hard to pinpoint with any certainty.

Is increased cognition the desire of the primary researchers of the DFSS? Maybe, but this seems unlikely as they confound the idea of CE in healthy individuals with the need to develop treatments for those individuals suffering from Alzheimer's disease and mild cognitive impairment[1]. Thus the context of their desire to increase cognition seems to be less focused towards individual and societal gain than it is on restoring previously held faculties. Has the desire for drugs for intellect arisen from the media reflecting and disseminating the interests of the public, as has been described elsewhere [56]? Again, this is a possibility, yet there is little empirical evidence that the general public is truly interested in CE[2]. The only clear supporters of increasing intellect through enhancement technologies are those bioethicists and theorists who actively argue that greater intellect

---

[1] *See* chapter 1 discussion, under *Case study of donepezil*
[2] *See* the discussion on prevalence in chapter 1, notably [6, 7] for examples.

promises a better society[3]. Yet, even these academics allow that there is little evidence that higher intellect will lead to greater happiness. In the absence of a primary desire by the majority of individuals for this effect, it is possible that rather than reinforcing the goals of the majority the CE debate, and its media coverage, is perpetuating the views of a minority and driving the perception that this is the majority view [6, 70].

The need to better understand the broad social forces shaping the CE debate calls for perspectives that provide new lenses through which we can better understand and critically examine the values it upholds and perpetuates. In Chapter 3, we discussed the potential for hype of CE drugs to generate social pressure to increase intellect and highlighted that such pressure may influence individual decisions, autonomy, and clinical care. We also raised the potential problem of a lack of social and cultural diversity resulting from conformity with the desire to increase cognition [8, 54]. Finally, we introduced the possibility that hype of the assumed beneficial effects of increased intellect, which is being propagated through the CE debate, could negatively affect individuals with intellectual disabilities (ID). In this general discussion, we now turn to focus on this specific repercussion of hyping the desire to increase intellect by using a disability ethics lens to further consider the effects of the CE debate. A disability ethics perspective, which to our knowledge has not yet been extensively considered in the CE debate, [4] could yield new understandings of the current debate and its social consequences, as well as promote a novel approach to the consideration of ID by society.

In order to disability ethics to the broad discussion of the implications of the CE debate, we describe a related but distinct case of media hype regarding the possibility of increasing intelligence through novel pharmaceuticals, but this time with respect to individuals with ID, specifically with ID associated with fragile X syndrome (FXS). By first comparing the trends found in the reporting of the DFSS in the CE debate with the current framing of drugs targeting ID in FXS by the media and academia, we draw a connection between these two pharmaceutical trends and bring to light the similarity between the hype and social attitudes surrounding potential pharmaceuticals for CE and

---

[3] *See*[21] as an example.

[4] Although present at the beginning of the more general debate on enhancement see Silvers [87] for initial arguments on this topic and McMahon [88] for an approach to this issue from a different angle.

those for ID. We then bring a disability rights perspective to bear on the treatment-enhancement distinction, revisiting fundamental concerns regarding the distinction that are often overlooked to underscore its limitations with respect to upholding human diversity. Finally, we consider the current management of ID in light of these limitations of the treatment-enhancement distinction, arguing that by primarily considering it within the treatment framework we may be limiting the ethical consideration of the merits of pharmaceuticals that target intelligence as a means to improving quality of life and could be subverting positive social movements. Of course, this general discussion can only provide a cursory exploration of the connection between the CE debate and pharmaceuticals developed to increase intellect in individuals with ID and is therefore unable to address other important issues such as research ethics concerns related to clinical trials for these drugs, the use of efficacious animal models driving the drug development, and the commercial influence of pharmaceutical companies.

Hype, enhancement and "ideologies of intellect": Bridging CE and disability ethics

The current example of drugs for FXS[5], a genetically based neurodevelopmental disorder that is the leading inherited cause of ID, is of particular salience to our discussion of CE and the DFSS case because these new drug developments have generated hype in both the media and academic circles, reflecting our findings with respect to donepezil and the DFSS. However, there is one main difference in how these two cases are portrayed: the discussion of increasing intellect in the DFSS case study is part of a debate over the merits of CE. The discussion around increasing cognition in

[5] FXS is the most common form of inherited ID [89]. It is an X-linked neurodevelopmental syndrome caused by a trinucleotide repeat sequence (CGG) on the FMR1 gene, which in the "wild type" exists as less than 40-50 repeats. Individuals who have between 55-200 repeats are known as premutation carriers and are able to pass the mutation on their children, with the chance of it replicating in transmission to present as a full mutation with more than 200 repeats. It is with greater than 200 or more repeats that individuals are diagnosed as having FXS [90]. At this level of repeats the sequence is hypermethylated (silenced) and the associated protein (FMRP) is not produced. FXS affects approximately one in 4000 males and one in 8000 females, while approximately one in 300 women and one in 800 men carry permutation alleles that may also cause related conditions such as primary ovarian insufficiency (FXPOI) or fragile X tremor ataxia syndrome (FXTAS) [90]. FMRP plays a role in the negative regulation of downstream protein production. Without it, later proteins are over produced contributing to hyper signaling or stimulation at the neural synapse. This lack of an inhibitory effect is what is said to account for ID, specifically learning and memory related components, in individuals with FXS, giving it the lay description of a "disorder of excess" (Bear, in [91]).

individuals with FXS is taking place exclusively in the medical realm, with the drugs being lauded as revolutionary treatments. In spite of their differing frameworks, both cases bring forth similar features of hype and rest on the assumption that increased cognition will be unilaterally beneficial.

The story of FXS is especially applicable to our discussion of misrepresentation and media hype, as the discovery of the FMR1 gene[6] in 1991 was intricately tied to the Human Genome Project (HGP), a project widely hyped to develop cures for genetic disease [92, 93]. The isolation of the FMR1 gene was an early success, and was used to validate the large monetary investment the project required[7]. With the incredible funds poured into the HGP and the world watching, the idea that it would lead to medical advancements for disorders such as FXS was widely publicized. The public message was that the HGP was a "Holy Grail" [94] opportunity, of which the research could "prove miraculous and good for everyone" [57, 94][8].

Until recently, the reality of a miracle cure for ID associated with FXS has been elusive at best. Indeed, the popular clinical view has historically been that ID is "immutable" [90], "irreversible or untreatable" [96]. However, circa 2004 there was renewed interest in the possibility of treating ID as animal models provided knowledge about the molecular pathways involved in ID associated with FXS. It is now hypothesized that currently accessible drugs such as mGluR inhibitors, ampakines, GABA agonists like STX209, and antibiotics such as minocycline could target these intracellular pathways, limiting their effect on cognitive processes[9][90, 97]. Several of

---

[6] *See supra* note 5

[7] One of the leaders of the project reportedly argued, "every year, 2000 boys are born with Fragile X syndrome who will re-quire care for the rest of their lives, at a minimum cost of $100,000 each. That puts the burden of the disease at $200 million a year… and that's just what has been requested for the genome project" [93].

[8] This public goal was alternate to the private goal of economic benefit and an increase in biological knowledge that was implicit within the HGP [57, 95]). It seems that the HGP had a dual use: "though disease genes captured the public imagination and kept the dollars flowing, this project was designed to build the equivalent of a particle accelerator" [95].

[9] These drugs are part of a "mechanism-based approach" [90]. The goal of is to limit the amount or effect on the increased synaptic protein that is present due to the lack of FMRP [97].

such experimental pharmaceuticals are currently being tested in clinical trials[10] [90, 96], fuelling excitement in both the media and academia.

Similar to the hype raised in media and bioethics articles with respect to the findings of the DFSS, media and academic attention to these drug developments demonstrates high expectations for a drug to improve cognition, as well as promoting this drug effect despite limited proof of efficacy. Lauded as "a "sea change""[11][96] and "a paradigm shift for central nervous system… drug development" [90], researchers have described the novel application of these drugs as a means "to realize the mission of implementing effective treatments of ID" [90], which was previously considered to "cause such devastating and complex consequences for patients [with FXS]…that many concluded the damage was permanent" [96]. The media picked up these academic developments early on, donning headlines that read "Promise Seen in Drug for Retardation Syndrome" [98]. The notion that these drugs may allow us to "reverse the retardation"[12] [91] was widely heralded, with researchers being quoted to state that "[p]eople haven't thought what it would be like to reverse intellectual disability or mental retardation, we now think it may be possible" [99]. In light of our knowledge of the CE debate and the claims hyped regarding the potential effects of donepezil in the absence of efficacy data, it is not surprising to note that there is currently a dearth of evidence supporting these claims as well[13].

In June of 2010, a *Nature Neuroscience* editorial criticized the *New York Times* for reporting this story in the absence of sound evidence. Specifically, they condemned the reporting of "a promising outcome from a small-scale clinical trial" [100] when neither the specific results of this trial nor "the critical details" [100] had been formally released. The drugs still have to pass "the biggest hurdle" [100] of phase III trials before they will be approved for this purpose. By presenting only a general description of the results, the scientific community is unable "to independently examine the data and

---

[10] *See* http://www.clinicaltrials.gov/ct2/results?term=fragile+x+syndrome for a complete list of current trials.
[11] This quote is attributed to the researcher Bear, in [96]
[12] This quote is attributed to the physician- researcher Hagerman, in [91]
[13] The current body of evidence supporting these claims is linked to animal models, mice and fruit flies. See [96] for references.

critically evaluate whether the preliminary results are indeed promising" [100]. In fact, even the media article states: "[t]he Novartis trial, which began in 2008 in Europe with data analysis completed this year, was too brief to observe effects on basic intelligence"[98]. Subsequent academic discussion of the effect of these drugs has further noted that the results may not be as good as they were presumed to be, and may even have negative effects on individuals—calling the theory behind the presumed drug effect into question [101].

The language of a "reversal" as the goal of these drugs also stands out as problematic. Certainly the drug effect claimed is not really a reversal, but would be better described as an *inducement* of what is considered to be a "normal" or ideal state. Elliott has discussed this phenomenon as he sees it applied to transsexuals. He writes that the change undergone by transsexuals is often described through a "restitution narrative"[14][102], yet "the restitution is to something that never existed before, only wished for—not restoration back to health, but restoration to an ideal of health that had never before been realized" [102]. This describes both the language and the intention of the desire to "reverse the retardation," with one small, yet significant, difference: the "wished for" change is not necessarily wished for by individuals with FXS. And, without discussing the specific effects of the drugs, parents are left to wonder what the "undisclosed" [100] effects of the drugs are and "whether this new drug works better than existing ones" [100], as they take on the momentous responsibility of considering whether to enrol their children in clinical trials or request the drug off-label in an effort to improve their child's quality of life.

Though considered to be two distinct applications of pharmaceuticals developed to treat intellect, the general discourses that underlie the discussion of donepezil as a CE agent and novel drug treatments for ID seem to fall prey to the same aphorism: to laud improvements in intellect in spite of scientific evidence or clearly articulated drug effects. The similarity between media and academic hype of so-called CE drugs such as donepezil and novel pharmaceuticals reported to treat ID calls for a closer look at the treatment-enhancement distinction. The following sections demonstrate that relying on

---

[14] A term attributed to Frank in [102]

the treatment-enhancement distinction to determine what medications are viewed as necessary for individuals and what medications we debate the social merits of may be limiting the ethical deliberation surrounding this novel drug development. Moreover, we underscore the potential for media and academic hype of the value of increased cognition (whether within or external to the CE debate) to wittingly or unwittingly contribute to the further devaluation of individuals with ID.

Limitations of the treatment-enhancement distinction with respect to human diversity

Our study of the reporting on the DFSS (Chapter 3) demonstrated the confusion inherent in distinguishing the acceptable use of a medication by employing the treatment-enhancement distinction. Donepezil was lauded as an enhancement agent, though it is unclear whether the DFSS was designed to determine enhancement or treatment effects, due to confusion surrounding whether their study subjects were "diseased" or "healthy". Subsequently, the alleged CE effects of donepezil were hyped to the detriment of clearly reporting the discrete findings of the DFSS or articulating the precise drug effect. The development of drugs for ID in individuals with FXS presents a similar "framing" problem: the connection to cognition is being hyped in media and academic articles, while a discussion of the targeted drug effects, and their possible role in supporting individuals with ID, is overlooked. However, in this case hype is being generated around the drugs while they are discussed as treatments, rather than as enhancements. It is commonly assumed that "a drug to improve cognitive function in persons with below-normal cognitive ability… would not be considered an enhancement" [103], and thus should be viewed as a treatment. Yet, the justification for this classification is not necessarily sound and may negatively affect individuals with ID as individual context, discrete drug effects and wider social impact are overlooked. A cursory review and critique of the original arguments that position disability (as a homogeneous group) within the treatment category, provides background for why the current consideration of drugs for ID associated with FXS within this dichotomy may be problematic.

As we discussed in Chapter 1, the treatment-enhancement distinction is typically based upon the assumption that a medication that targets a disease or disability is

necessarily beneficial and thus individuals with disabilities should have access to them. In light of the human genome project, Daniels further developed this argument. He considers, "disease and disability are… departures from species-typical normal functional organization or functioning" [17] and, because "[n]ormal functioning is a crucial determinant of the opportunities open to an individual" [17] any intervention developed to provide "normal functioning" ought to be provided as health care. Thus, any such interventions should be considered treatments, as opposed to enhancements. Specifically, "characterizing medical need [as a departure from normal functioning] implies a contrast between medical services that treat disease (or disability) conditions and uses that merely enhance human performance" [17]. In this way, interventions that target any condition considered to be a disability are seen as treatments. However, this delineation of the boundaries of health care is based on what Silvers calls a macro orientation to the role of health care. Within a "macro-(bio)medical ethics" framework, ethicists work to delineate "how to judge right and wrong in caring for patients… by proposing what kind of health care…a just society allocates" [87]. Thus, it makes-up a "top-down" approach to determining what "the right interventions" [87] are for individuals. The priority is to determine how to justly allocate services *broadly*; yet, the practical consequences of such a process inevitably impact individual care.

Of interest, worked into Daniels' famous, "hard-line" [20] distinction is the understanding that part of the reason behind drawing this line is a commitment to "preserving differences" [20]. As explained by Parens, it is not Daniels' goal to "replicat[e] specific forms of function" [20]. Indeed, he believes the treatment-enhancement distinction should help us ensure that "natural differences and characteristics that medicine ought not to be used to erase" [20] do not become a target of medical intervention. Thus, in addition to providing opportunity through the just distribution of resources, the treatment-enhancement distinction also has the goal of preserving the landscape of diversity. In light of its impact on individual care, this secondary goal is praiseworthy. However, the ability of the distinction to uphold this additional intention while relegating all drugs that target disability to the treatment category is questionable. We will explain our concern by revisiting the example that Parens used to demonstrate the distinction's potential.

Parens' essay underscores Daniels' commitment to preserving diversity, by explaining Daniels' response to a scenario presented by Allen and Fost[15]. In their scenario, they ask how one would determine who to provide treatment to if one was faced with a boy who would grow to be 5 feet, 3 inches tall due to the presence of a brain tumour that was causing a deficiency in growth hormone and a second boy who did not have a deficiency in growth hormone, but had very short parents and thus was destined to grow to only 5 feet 3 inches as well [20]. Daniels' response was to treat only the former child, on the grounds that the child is suffering from a biomedical problem, which reflects a medical need that the public can agree upon, while the latter child is not [17]. Further, as Parens explains, to treat the latter child would be to "undermine our fundamental commitment to preserving differences, to promoting the health of populations made up of people whose normal function takes different shapes" [20].

There are two potential problems with this argument. First, it casts growth hormone deficiency as the biomedical disease suffered by the first child. Though a change in the individual's predicted height, which has certainly been caused by a disease, the disease the child suffers from is really the brain tumour, not short stature. Thus, to treat the deficiency in human growth hormone seems to be a second choice, failing treatment of the brain tumour. Of itself, the growth hormone deficiency only becomes a disease as long as we are concerned with short stature. Without social prejudice towards height, a decrease in growth hormone will not cause the first child any health problems. And, if we are to assume that the change of this child from his expected average height to a shorter stature will limit his range of opportunities, then we have undermined the logic upholding the decision not to treat the second child. That is, that short stature is part of the normal range of diversity, which should be preserved. While an enhancement is described as something which "does not meet a medical need even where the service may connect to a competitive disadvantage that does not result from prior choices" [17], to treat short stature may be better described as an "enhancement," as we would really be addressing the social prejudice and competitive disadvantage prescribed to height.

---

[15] Cited in [17].

Second, by assuming that a measurable decrease in growth hormone accounts for a disease state, Daniels' argument draws a line between this type of biomedical problem and that which was inherited through genes passed on from the second child's parents to cause his measurable difference in height. As discussed in Chapter 1, social norms and standards have been known to shape what we understand to be a "disease state," and what we consider normal human variation[16]. Through the process of medicalization, factors of everyday life can come to be seen as diseases. What is interesting in this example, is that a decrease in human growth hormone is seen as a disease state, presumably because there is a clear and effective treatment option available (the provision of supplementary growth hormone), while the genetic, inheritable, aspects of short stature, are not. Thus, we may not be providing the second child with extra growth hormone because he is already producing a normal amount, but because we have not yet medicalized the genetic component of short stature to the degree that we have medicalized a reduction in growth hormone, a problem acknowledged by Daniels himself [17]. However, Daniels dismisses this concern, arguing that his goal is to be just in our distribution of health care and attending to biomedical differences allows us to do so as it "reflects *moral agreement* about the urgency of medical care" ([17], emphasis added).

He contends, "we are far less likely to think that it is "urgent" to correct the effects of these newly labeled "bad genes"," [17]. Thus, forgoing his model of health care distribution due to the potential for medicalization would "undermine agreement on the importance of meeting medical needs" [17], leaving us without a means "to draw a line" [17]. Thus, he concludes, "there is justification for adhering to a distinction that captures and sustains social agreement on important matters, even if the distinction seems arbitrary" [17].

Yet, the limitation of his argument becomes clear if we acknowledge that when it comes to diversity, attending to the views of the majority to determine which "biomedical needs" are "urgent" and which are not is not necessarily a just means of determining whether the diversity experienced by the individual in question is worth preserving. This becomes particularly problematic in the presence of medicalization as medicalization is

---

[16]*See* chapter 1, *Medicalization and the treatment-enhancement distinction*

also heavily influenced by social context. Thus, social prejudice can fuel both medicalization of a biomedical basis for unaccepted diversity as well as social consensus that the diversity in question represents a legitimate medical need. In this way, using the treatment-enhancement distinction as a tool to determine the acceptable provision of medication undermines the commitment to preserving social diversity: it allows society to address pervasive social prejudice through an available technical intervention. The only diversity that will be preserved by this method is that which does not stand out as being "diverse" at all.

Turning back to our example of novel drug developments that target ID, it seems that this "symptom," as it is being discussed in media and academic articles, deserves the same reappraisal as "short stature." The concept of ID emerged from negative social norms and persists today surrounded by stigma. Just as short stature is said to fall outside the norm at the height of 5'3" for males due to the use of a bell curve [104], so too is the normal range of intellect defined. When the DSM (The Diagnostics and Statistics Manual-dictionary of psychiatric disorders) was first written the diagnostic term "Mental Retardation" was included[17]. This diagnosis is determined mainly based on the results of intelligence tests, which rely on the bell curve. A test score of 70 represents a level of intelligence two standard deviations below the mean, defining the upper limit of the diagnosis [106]. However, the notion to use this distribution to classify ID as abnormal is itself heavily linked to social prejudice. The statistical methods involved in determining whether an individual's intellect lies within the "norm" are laden in value judgments as they were developed and implemented in conjunction with the science of genetics during the eugenics movement[18]. Thus, ID as a novel, targeted, biomedical impairment is difficult to separate from the subject of ubiquitous social prejudice.

---

[17] On the grounds that the term "Mental Retardation" evokes discrimination there is a proposal to change the diagnosis to "Intellectual Developmental Disorder" for the DSM-5 [105].

[18] As Kevles explains, modern genetics began with Galton, the British founder of eugenics, who coined the term in 1865 [107]. Drawing from the use of the bell curve—then known as the "law of error" [107]—in astronomy, Galton began to apply it to populations as a means to determine "error" in society, meaning variations in weight, height, and especially, intellect [107]. This application was made possible because the bell curve contains an area two standard deviations away from the mean of the curve [107]. What was found within this area of two standard deviations was perceived to be the standard distribution of qualities, making up the "normal" tendencies of a population, and the normal amount of variance within a

In addition to this history that initially acted to frame ID as a disease state, FXS was heavily "geneticized"[19] during the HGP. Now, as the previous section explored, ID associated with FXS has been framed as a genetic, and therefore treatable, disorder. The social prejudice associated with ID, as well as the geneticization of intellect as it has become intricately tied to the genetic basis of FXS, makes ID associated with FXS a key example of how medicalization, shaped by social context, can affect the way a condition is framed in the treatment-enhancement debate. Thereby, it acts as an example of where Daniels' distinction, though perhaps efficient when it comes to macro organization and the establishment of just access to resources[20], fails to preserve diversity. It supports the assumption that ID *necessarily* receive treatment without paying due attention to the

---

population. Anything that fell above or below represents "error". This use of the bell curve was quite different from its use in astronomy as a tool to determine which measurements were the true measurements of a physical property (the true measurement was assumed to be that which occurred with the greatest frequency, representing the mean) [107]. Besides applying this theoretical concept to the population, rather than to attempts at measuring astronomical distances that were susceptible to human error, where astronomy was interested in finding the mean Galton wanted to improve human ability and thus saw the normal as an average that was to be improved upon. If an individual fell above the mean, he was excellent and Galton sought to increase his frequency. His goal was to "[breed] for the highest order of intellect" [107]. This desire was carried through the eugenic movement, as Kevles summarizes: "Eugenicists, who were themselves predominantly of the old majority, considered scholastic intelligence—the kind indicated in I.Q. tests—a paramount measure of human merit, ignoring other abilities" [107]. This value-laden history has cast individuals with levels of intellect that fall two standard deviations below the norm as suffering a medical problem that requires "fixing."

[19] Geneticization is a term coined by Lippman in the early 1990's to describe the process where, by giving priority to genetics as the sole determinant of what "makes us what we are" [108], mappers in the Human Genome Project "condition[ed] how we view, name, and propose to manage a whole host of disorders and disabilities" [109]. As she explains, "[d]isorders and disabilities are not merely physiological or physical conditions with fixed contours. Rather, they are social products…Defining and studying these categories…is necessarily subjective, reflecting how those with power at any particular historical time construct them as problems" [109]. Through the process of geneticization, the genetic basis of FXS has been prioritized, "objectif[ying] the body and mak[ing] the genome, rather than the person, the focus of medical attention" [108]. The path to well-being is thereby reduced to identifying "an observed change in the shape/constituents of DNA" [108] and finding a means "to fix, replace or substitute" [108] it. In light of its connection to FXS, the relatively straightforward single-gene nature of the disorder, and the history of stigma that surrounds low intellect, it is not surprising that ID is being targeted as a disease state and is presumed curable through technological means.

[20] Daniels' macro approach to health care may be positive for individuals with disabilities if these drugs turn out to support individual interests and quality of life, as it seeks to provide them with access to health care. However, because this framework justifies the assumption that all drugs developed for a disability are *necessarily* beneficial to the individual, his approach is problematic—especially, since the "treatment" effect that is being hyped is increased intelligence and not a symptom that is free from the interaction of social prejudice, such as attention. While Daniels assumes that "[h]ealth care is not the only agent of social responsibility" [17], we argue in the following section that, unfortunately, though not the only agent of social responsibility, the values health care upholds provide the authority to potentially undermine other means of social betterment.

social context that has shaped the conception of ID as a disease state or considering the downstream implications of such a conjecture for individuals.

Understanding the social forces at play in shaping these drugs as praiseworthy treatments introduces doubt into the assumption that ID linked to a genetic structure is necessarily cause for medical intervention. Failure to account for the social factors involved in constructing ID as a disease state may have the same effect described with respect to geneticization, i.e., it may "incorrectly decontextualizes these technologies" [109] that aim to cure it, with potentially grave implications for social acceptance of and support for individuals with ID.

The subversive role of hype around intellect for an inclusive society

In Chapter 3 we discussed how the portrayal of donepezil as a CE agent hyped the benefits of increased intellect and explored the potential for such hype to drive social pressure to use drugs for CE (even in the absence of sound efficacy data). In the previous two sections, we outlined how novel drugs for ID associated with FXS are also being hyped in the media and academia as a result of their effect on intellect, yet are being lauded as revolutionary "treatments". In this final section, we explore the implications, for both individuals and society, of continuing to conceive of these drugs as treatments. We continue by proposing a means of moving forward in spite of the limitations of both the enhancement and treatment frameworks for inspiring positive social valuation and opportunities for individuals with ID.

The connection between ID, FXS, and the HGP may already be influencing the way we value and support individuals with this diagnosis. Lippman has identified that "[t]he search for a hereditary basis for… conditions and traits considered part of our rich store of human diversity is already casting many of these variations as abnormalities" [108]. Elliott has also commented on this phenomenon, articulating how what was once viewed as a different way of being, is now viewed as a disease state: "one spoke of dwarves, lunatics, imbeciles, mongoloids—a vocabulary that has now been transformed into one of illness. A person with three copies of chromosome 21 is no longer a mongoloid; she has a genetic disease, Down syndrome. Whereas we used to think of her as a different type of human being, now we think of her as sick" [102]. Two decades after

the isolation of the FMR1 gene, it is difficult to consider that someone with ID associated with FXS was once considered a mere part of the "rich store of human diversity," even more so to consider that they may simply be a "different type of human being". We are more likely to view a child born with this disorder "as (exhibiting) a 'failure'" [108].

This "failure" narrative stands out in the current media and academic attention to drugs for ID. Rather than presenting a balanced perspective of life with ID, the lives of individuals with FXS are fatalistically presented in these articles. The above mentioned *New York Times* article describes the spectrum of abilities associated with FXS as having "mental effects ranging from mild learning disabilities to retardation so profound that sufferers do not speak" [98]. The *LA Times* recently described FXS as "a train wreck of conditions—autism, attention deficit, bipolar disorder, anxiety and more—rolled into a single kid" [99]; *Chicago Parent* called it a "genetic landmine"[110][21]; and, the *Japan Times* followed a disastrous description of receiving a diagnosis of FXS[22] by identifying ID as the "cause of profound unhappiness in parents of children born with [it] as well as in the children themselves" [111][23]. Indeed, the example of FXS seems to be evidence that "geneticization [has given] [stakeholders in the HGP] tremendous power (and wealth) for defining how we think of ourselves and others and for determining who will manage us as individuals and as a society" [108], emphasizing the importance of critically examining the effect of classifying these drugs within the treatment framework.

Applying Bérubé's writings on justice for individuals with ID, such descriptions of the lives of persons with ID succeed in creating enthusiasm for these novel pharmaceuticals by upholding a "performance criterion" [112] that portrays acceptable ways of being. That is, they hype the benefits of these drugs, not by expounding on the discrete effect they might have on facilities considered important to the individual, but by

---

[21] Of interest the family interviewed for this article wrote a critical response related to this language use. The article was then removed from the site and subsequently re-posted, but without the "landmine" comment.

[22]Described as feeling "as if somebody had pointed a gun to me [a father's] head" [111].

[23] These descriptions are particularly hyperbolic when the lived experience of individuals with FXS are considered in more detail. For example, these articles often contain a statement such as this one: "Matt is the sweetest, most empathetic child I have ever seen… He is happy with the little things in life" [110]. Yet, these important glimpses into how individuals feel about their lives are easily overlooked when contrasted against such devastating introductory descriptors and framed within a discussion of *treatment* as a necessary means to improve quality of life.

drawing on the fact that currently, we lack an effective and widely-acceptable means of social organization capable of "support[ing] and nourish[ing] some people who will never be capable of returning the favor" [112]. Accepting the use of such a criterion in the current discussion of these pharmaceuticals allows those who set the criteria to determine the social value of individuals with ID and in this case, who we decide to treat. Rather than upholding the best interest, or person-first, standard common to bioethics, this means of generating interest in a medical technology works to the detriment of the individuals whom the drugs target: "any performance criterion—independence, rationality, capacity for mutual cooperation, even capacity for mutual recognition—will leave some mother's child behind. It will create a residuum of the abject, a fraction of the human family that is to be left out of the accounting" [112]. In this case, the performance criterion is a typical level of intellect. And, as Bérubé succinctly states: "[We] don't accept the premise that cognitive capacity is a useful criterion for reading some people out of the human community" [112]. Cognitive capacity is not a useful criterion for assuming a treatment will *necessarily* be to an individual's benefit, without duly exploring the effects of the treatment and the individual's unique context, which may make them applicable.

The expectation that individuals with ID will be "better off" with a typical level of intellect is a widely held expectation, but it is merely an expectation that is, too often, assumed to be true based on years of oppression. What dimensions of well-being individuals with ID have access to can only be known by the individual herself. The only thing typically functioning individuals can be certain of is that "we honestly—if paradoxically—don't know what constitutes a "reasonable expectation" for a person with [ID]" [112].[24] Disability rights advocate, Asch, further argues this point, stating, "[t]he child who will have a disability may have fewer options for the so-called open future that philosophers and parents dream of for a child. Yet I suspect that disability precludes far fewer life possibilities than members of the bioethics community claim" [113]. As such, inducing a new level of intellect through pharmaceutical use may be the wish of parents,

---

[24] Moreover, we do not know if one is truly happier with more dimensions of well-being than with less. In light of the magnitude of the current debate around CE amongst individuals with typical intellect, it seems questionable whether the "typical" level of intellect really makes a more content individual.

physicians, or researchers, whose expectations for these children reflect "an ideal of health" which is presented, and glorified, as integral to a good life and sustained as important through the choices we make when it comes to supporting the lives of individuals with disabilities on a daily basis. Yet, we must recognize that their intentions may have been formed by pervasive and historical social prejudice, and may not reflect the needs and desires of individuals with FXS.

Embracing the "treatment" framework for drugs that target ID associated with FXS we risk limiting our discussion of ID to a medical one. The geneticization literature is rich with discussions of how such a technical framework can be a detriment to socio-political action to address the social causes of reduced opportunities, which may be a more just manner of ensuring quality of life for people with ID. As McDonough argues, considered within the treatment framework, "the 'problem' of disability is located in the individual, rather than in the social, political, and economic context that devalues individuals with disabilities and restricts their participation in society" [114]. By placing the responsibility of managing disability on the individual, or in this case, the parents, "the model may be coercive," [109] making individuals responsible for "adverse social circumstances" [109]. As a result, the treatment framework may "se[t] the stage for social control and for 'victim blaming' of those who don't follow" [109], potentially limiting stakeholders' perception of the option to forgo the unknown risk associated with these poorly described, and yet unproven, pharmaceuticals[25].

Furthermore, in this framework no credence is given to the possibility "that *society* has malfunctioned because it cannot accommodate [individuals with disabilities] in its midst" [108]. Yet, disability rights activists have stressed, "disability does not preclude a satisfying life. Many problems attributed to the existence of disability actually stem from inadequate social arrangements that public health professions should work to change" [113]. Thus, it may be that the stigma surrounding ID introduces a greater burden on quality of life for these individuals than their level of intelligence itself. This

---

[25] Social pressure on individuals which may include pressure on parents—often exacerbated by media or academic hype of treatments—has precedence in genetic screening technologies where "the pregnant woman [i]s obligated to produce a healthy child…she is expected generally to do everything possible for the fetus…This technology perversely creates a burden of not doing enough, a burden incurred when the technology is *not* used" [109].

calls into question the benefit of bio-medical research that seeks to cure biological impairments that are seen as individual problems due to their association with pervasive social prejudice. Indeed, taking from the precedent of questioning genetic screening technologies, "arguing that social changes are "needed" to enable those with malformations to have rich lives is not an inherently less appropriate approach [then a technical intervention]. Actually it may be more appropriate, since malformation, a biomedical phenomenon, requires a social translation to become a 'problem'" [109]. Though often assumed to be "intractable givens" [109], social conditions are mutable. Because "[s]ocial conditions are as enabling or disabling as biological conditions" [109], a broader focus on resource allocation alone could begin to improve the quality of life of these individuals[2627]. However, these practical concessions do not fully address the more fundamental and challenging problem of reducing historical social prejudice against individuals with different levels of intelligence. Attention to this more pervasive need is both necessary and possible.

Stakeholders in the disability community have already begun the process of challenging the persistent stigma surrounding cognitive disability. In 2009, Special Olympics began the movement to reduce the use of the word "retard(ed)" [116] in both academic and lay speech to increase positive valuation of individuals with ID[28]. Autistic individuals have begun campaigning for "neuro-equality," [118][29] which they define as

---

[26] *See* [115] for a summary of what factors are known to influence an individual's quality of life. Of note, interpersonal relations and social inclusion were found to be the most common individual-referenced quality of life domains, which describe the importance of interactions, relationships, supports (financial, emotional, and physical), and community integration, having a role within the community, and having social supports, respectively (from Tables 1 & 2, pgs.205-206).

[27] Lippman argues that prenatal technologies have been justified through a discourse of "reassurance." Yet, she contends, and we see her point applicable here, that there are other means of reassurance: "allocation of funds for home visitors, respite care and domestic alterations would "reassure" women that the resources required to help them manage their special needs were readily available without financial cost" [109].

[28] Following the initiation of this campaign, President Obama signed a law to ensure the language was no longer used in United States statutes. A recent bill in Saskatchewan argues that similar steps are needed in Canada [117]; *see supra* 17 on the effect of this movement on proposed changes to the DSM5.

[29] "[T]hough neurologically, cognitively, and behaviourally different, [the neurodiverse] do not necessarily suffer from being neurodiverse nor do they need to be cured" [118]. The movement is "associated with the struggle for the civil rights of all those diagnosed with neurological or neurodevelopmental disorders" [118]. They argue for a reconceptualization of what it means to be functional to reflect a measure of "human flourishing" [118]. Such a sense of functionality would accept individuals as functional so long as they have "contentment, self-worth, confidence and personal achievement" [118].

the right to diversity without the threat of a "cure." [30] And, the Down syndrome community, which is also a target of these novel drug developments for intellect [96], has taken a radically alternative approach to increase quality of life for individuals with ID. For example, comparison of leading websites for the Down syndrome and FXS communities demonstrates that there is a disjunction between how these two disorders are approached and managed. Where the focus of the Down syndrome websites is on advocacy and acceptance of diversity, the FXS websites present a strong voice in favour of research for a cure[31]. Clearly, there are other means of attending to the well-being and quality of life of individuals with ID than through the application of a narrowly focused treatment plan. Indeed, by targeting intellect as a problem for individuals, these drug developments risk subverting some of these most recent and revolutionary approaches to improving their quality of life. It undermines the principled stance these movements are based on; specifically, that a typical level of intellect is not necessary to a flourishing life[32]. In this case, it also risks subverting the social gains that have been brought thus far by these movements.

Additional concerns related to increasing intelligence, which have been raised through the CE debate, are also being overlooked in current discussion of these drugs to the potential detriment of individuals with FXS and ID more broadly. Specifically, examination of the coverage of ethical issues in the enhancement debate demonstrates that attention to both individual ethical issues, as well as broader social concerns is

---

[30] For example, Temple Grandin, an autistic researcher, has famously stated "[i]f I could snap my fingers and be nonautistic, I would not—because then I wouldn't be me. Autism is part of who I am," Grandin in [119]; *See*[120] for a detailed discussion of the ethics of proposing a cure for autism.

[31] Consider the message of the home page of the Fragile X Research Foundation of Canada: "The Fragile X Research Foundation of Canada is dedicated to raising awareness of and funding research for [FXS]—the most common inherited form of mental impairment in the world. While [FX] individuals have a normal like expectancy, most individuals will need support and care for their entire lives—a key reason why a cure is so imperative" [121]. The message conveyed is one of economic burden requiring a medical solution and stands in stark contrast to the message in support of advocacy, social inclusion, and the need to uphold the values of equal opportunity and respect, which is the focus of websites such as the Canadian Down Syndrome Society. Specifically, their vision is "[a] proud Canada, where ALL are welcome, we embrace diversity and we value everyone equally" [117].

[32] The problem of subverting social movements has been previously articulated by Lippmann and McDonough, who argued that giving technological approaches "priority diminishes incentives to challenge the existing system… the genetic approach… seems to provide a 'quick fix' to what is posed as a biological problem, directing attention away from society's construction of a biological reality *as* a problem and leaving the "conditions that create social disadvantage or [disability]… largely unchallenged" [114]" [109].

currently lacking. Individual ethical issues such as the effect of these drugs on one's personality, sense of identity, authenticity, or the role of happiness for a good life, are not currently addressed[33]. As Elliott explains: "[m]uch deeper questions seem to be at issue when we talk about changing a person's identity, the very core of what that person is. Making him smarter… transforming him into a new person" [102]. Introducing a change in an individual's intellect may be considered as an effect on a fundamental trait that one may not be comfortable changing [69], raising crucial questions regarding whose interests are being fulfilled by these interventions. Additional issues such as paternalism, which further necessitates careful consideration of "questions about coercion, decision-making capacity, and levels of benefit" [12] are also brought to the forefront if we consider these drugs within the ethical purview currently applied to enhancements.

Further, due to the presence of the historical "broad context of devaluing" [123], drugs designed to counteract the effects of ID should come under ethical scrutiny for complicity with negative social norms, which has been argued as crucial for our endorsement of enhancement technologies. Little explains that when a medical technology is evoked to overcome a negative, or unjust, social norm[34] its use requires grave consideration as it risks being complicitous with the norm itself. To be complicitous is defined as "to bear some improper moral relation to the evil of some practice or set of attitudes… when one endorses, promotes, or unduly benefits from norms and practices that are morally suspect" [123]. One may be complicitous "not just when one subjectively endorses the suspect system, but when one's actions in fact end up reinforcing it" [123]. Due to the "*meaning* that these [interventions] carry for others" [123] and because "meaning emerges… as a function of a broad context" [123] Little argues that suspect norms may be unwittingly legitimized by a well-intended intervention: "others see in them a legitimization of or pressure to meet norms" [123].

---

[33] *See* Bolt, [122], for an overview of these ethical issues.

[34] Intellectual ability may be viewed as a negative social norm based on Little's distinction between those norms which are "convergences of idiosyncratic preferences, tastes, fads, and fashions" [123] and norms which should be considered "part and parcel of an unjust social ideology" [123]. The content of these latter norms is morally suspect because they are "grounded in… a broader system of attitudes and actions that is in fact *unjust*" [123].

Thus, when a negative social norm, such as that associated with ID[35], is present, which may be reinforced by the intervention in question, in this case novel drugs for ID, Little contends that the provider is not justified in their act by the claim that they are helping to relieve an individual of the distress caused by this norm. Simply put, "purity of motive" [123] does not suffice "to insulate actions" [123].

Little extends this analysis to discuss how the involvement of medical technology in a system of attending to, yet reinforcing, negative social norms can be seen as an additional threat to a just society. Because of medicine's high status, and due to the risk that may be involved in interventions, or in the research that goes into developing them, the involvement or support of the medical community "can easily be regarded as sanctioning the importance and appropriateness of those norms" [123]. Discussing the danger that can come from social perceptions on the authority of medicine, Little's argument supports that of the disability rights activists cited above. She explains how it is of the utmost importance that those involved refocus their attention to include a holistic appraisal of the social context within which requests for enhancement take place, rather than solely focusing on the morality of an individual intervention. Failure to do so gradually constricts "the options [individuals] imaginatively conceive for themselves" [123].

Evidently, applying a technical solution to ID may "circumvent but will not solve the 'problem'" [109] individuals with ID encounter because the focus of these novel medications is on a medically (genetically) constructed "disability, not on society's discriminatory practices" [109]. Greater awareness of the social factors that negatively contribute to the quality of life of individuals with ID may bring attention to novel methods and movements of valuing and providing opportunity to these individuals. Finally, applying the range of ethical deliberation found in the enhancement debate to these novel drug developments may help to ensure we take heed of these concerns.

---

[35] *See supra* 34

Conclusions & recommendations

The hype surrounding CE as seen in media and bioethics article's coverage of the DFSS, which lauds the possibility of increasing intellect irrespective of scientific evidence of efficacy or clear conceptions of what the discrete effects of such pharmaceutical use will be, is reflected in current media and academic discussions related to the novel application of pharmaceuticals to increase intelligence in individuals with ID, specifically in the example of FXS. In the case of donepezil, the messages conveyed depict a great desire for this effect, yet it is unclear whose desire it is. Similarly, drugs for ID are fuelling excitement amongst academic researchers, clinicians, and parents, yet the desires of the individuals themselves, as well as questions such as "do *they* have a right to decide whether or not to use these drugs?" are currently unaddressed. Determining who has an interest in these drugs, and what use ought to count as acceptable, or further *beneficial*, to both individual well-being and wider social concerns remains to be established.

Relying on the treatment-enhancement distinction to determine what drug interventions are assumed to be beneficial to an individual is not suitable when considering drug use for conditions that have been heavily medicalized and are connected to pervasive social prejudice. The dichotomy fails to uphold the social goal of preserving diversity. Within the "treatment" framework, drugs for ID are being lauded as necessarily beneficial, with the potential effect of undermining social movements, driving complicity with negative social norms, or overlooking fundamental individual concerns such as identity. Due to the limitations of the treatment framework, arguing to move our discussion of these drugs into the enhancement domain is tempting. Yet, considered as an "enhancement," donepezil is driving interest in CE and propagating the assumption that more cognition equates to a better life. Thus, to consider these novel drugs as enhancements may further perpetuate the already widespread hype that these drugs are necessarily beneficial to improving quality of life for individuals with ID.

In this chatch-22 position we propose that greater emphasis on the context of drug requests as well as the specific, and individual, benefits that these drugs may have on individuals be considered as the primary basis for their availability and ethical acceptance, whether the drug is donepezil or a novel drug for FXS. Reducing hype of the

idea that intellect is necessary to a good life should help rein in both these discussions, limiting actual requests to those based on a level of need that ought to be addressed. In addition, applying in depth ethical deliberation to the effects on identity and complicity will support person first social movements and an inclusive society that enables opportunity to all individuals. Finally, taking a page from the enhancement book and granting individuals with ID the right to see these drugs as additions to *their* typical way of being, such that they may exist without any treatment and still be considered part and parcel of the range of diversity that we are proud to have within our society, especially within the Canadian context where we uphold the values of inclusion and pluralism, will enable informed and available choice and help counteract coercion and "victim blaming."

The promise of CE raises important concerns for us all. To overlook the impact on of this phenomenon on individuals with ID risks further oppressing their opportunities and ability to flourish in society. By exploring CE through the disability literature, we have demonstrated the need to engage in the CE debate on a more holistic level. There is a need to critically examine the messages conveyed in the media and academic literature for what they tell us about the type of society we live in and what type of society we want to become. We need to openly question these expectations and desires to ensure that an interest in progress does not threaten the possibility of different ways of being; or, potentially more dangerous, does not oppress or devalue certain lives.

CONCLUSION

This thesis examined the power of the CE debate to transform an Alzheimer`s drug into a so-called CE agent. The hype surrounding this phenomenon indicates high expectations for CE, and acts to promote the benefits of increased cognitive capacities in the absence of evidence that such an effect is possible; or more importantly, is internally valuable to a good life.

In Chapter 3 we characterized the complex interaction between the presence of the CE debate, the authors of the primary study, and the secondary literature produced by the media and bioethicists that has contributed to this movement. We highlighted the potential for hype of CE, in this case generated by a reconceptualization of donepezil, to increase social pressure to perform at an idealized level. Specific implications of hype and social pressure were outlined; namely, the possibility of compromising individual autonomy in decision making by subverting a discussion of the targeted effects of these drugs, and the potential to shape public policy. Due to the involvement of the primary study in the conceptualization of donepezil as a CE agent and the potentially harmful effects of social pressure on the clinical context, we called for an expanded review process that would consider the level of evidence offered by small-scale primary studies before generalizations were made, as well as for the development of guidelines to introduce a means of accounting for social factors in the clinical context.

We followed up this specific discussion of the potential implications of the hype surrounding the idea that donepezil is a CE agent, by exploring the broad implications of hype around increased cognition. Drawing from both our empirical study and disability studies literature, we argued that discussing drugs that target cognition within the enhancement framework indiscriminately lauds their (presumed) effect. Similarly, considered within the treatment framework, drugs for intellectual disability are assumed to be beneficial despite sound evidence of an effect and without regard to the desires of the individuals the drugs target or the historical influence of social prejudice towards this population.

Evidently, there is a need to re-evaluate the current means of attending to the ethical issues raised by these drugs through the dichotomous treatment-enhancement distinction. Rather than create a critical and reflexive space that upholds individual and social interests, both frameworks wittingly or unwittingly support the idea that increased

cognition is integral to a good life, potentially devaluing individuals with intellectual disability and undermining the possibility of a truly accepting and diverse society.

Adjusting our focus away from defining the acceptable limits of the enhancement framework and towards a critical examination of the social values that this debate reinforces and perpetuates will help us begin discussing the factors driving the perception that there is a widespread interest in and need for these pharmaceuticals. Only by attending to these underlying issues can we begin appropriate ethical consideration of how these drugs may affect the lives of individuals and establish sound parameters for pharmaceutical use (based on known, and targeted, levels of efficacy) that are complimented by social movements to empower individuals of all intellectual abilities.

REFERENCES

1. Pfizer Canada Inc., *Product monograph: Aricept (donepezil hydrochloride) (revised June 25, 2007)*. 2007, Author. p. 1-51.
2. Forlini, C. and E. Racine, *Disagreements with implications: Diverging discourses on the ethics of non-medical use of methylphenidate for performance enhancement.* BMC Med Ethics, 2009. **10**: p. 9.
3. Birks, J. and R.J. Harvey, *Donepezil for dementia due to Alzheimer's disease.* Cochrane Database of Systematic Reviews, 2006(1): p. CD001190.
4. Gonon, F., E. Bezard, and T. Boraud, *Misrepresentation of neuroscience data might give rise to misleading conclusions in the media: The case of attention deficit hyperactivity disorder.* PLoS One, 2011. **6**(1): p. e14618.
5. Outram, S. and E. Racine, *Examing reports and policies on cognitive enhancement: Approaches, rationale, and recommendations.* Accountability in Research, in press.
6. Lucke, J.C., et al., *Weak evidence for large claims contribute to the phantom debate.* BioSocieties, 2010. **5**(4): p. 482-83.
7. Lucke, J.C., et al., *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): p. 197-201.
8. President's Council on Bioethics, *Beyond therapy*. 2003, President's Council on Bioethics/Harper Collins: Washington, DC. p. 328.
9. Repantis, D., O. Laisney, and I. Heuser, *Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: A systematic review.* Pharmacol Res, 2010. **61**(6): p. 473-81.
10. de Jongh, R., et al., *Botox for the brain: Enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories.* Neurosci Biobehav Rev, 2008. **32**(4): p. 760-776.
11. Yesavage, J.A., et al., *Donepezil and flight simulator performance: Effects on retention of complex skills.* Neurol, 2002. **59**(1): p. 123-125.
12. Juengst, E.T., *What does enhancement mean?,* in *Enhancing Human Traits: Ethical and Social Implications*, E. Parens, Editor. 1998, Georgetown University Press: Washington.
13. Hall, W., *Feeling 'better than well'.* EMBO Rep, 2004. **5**(12): p. 1105-9.
14. Farah, M.J., et al., *Neurocognitive enhancement: What can we do and what should we do?* Nat Rev Neurosci, 2004. **5**(5): p. 421-5.
15. Merkel, R., et al., *Intervening in the brain: Changing psyche and society*. Ethics of Science and Technology Assessment. Vol. 29. 2007, Berlin: Springer.
16. Whitehouse, P.J., et al., *Enhancing cognition in the intellectually intact.* Hastings Cent Rep, 1997. **27**(3): p. 14-22.
17. Daniels, N., *The genome project, individual differences, and just health care*, in *Justice and the Human Genome Project*, T.F. Murphy and M.A. Lappe, Editors. 1994, University of California Press: Berkely. p. 5-13.
18. Katz, S. and K.R. Peters, *Enhancing the mind? Memory medicine, dementia, and the aging brain.* J Aging Stud, 2008. **22**: p. 348-355.
19. Sabin, J.E. and N. Daniels, *Determining "medical necessity" in mental health practice.* Hastings Cent Rep, 1994. **24**(6): p. 5-13.

20. Parens, E., *Is better always good? The enhancement project*, in *Enhancing Human Traits: Ethical and Social Implications*, E. Parens, Editor. 1998, Georgetown University Press: Washington.
21. Sandberg, A. and N. Bostrom, *Converging cognitive enhancements.* Ann N Y Acad Sci, 2006. **1093**: p. 201-27.
22. Chatterjee, A., *Cosmetic neurology and cosmetic surgery: Parallels, predictions, and challenges.* Camb Q Healthc Ethics, 2007. **16**(2): p. 129-37.
23. Chatterjee, A., *The promise and predicament of cosmetic neurology.* J Med Ethics, 2006. **32**(2): p. 110-3.
24. Chatterjee, A., *Cosmetic neurology: The controversy over enhancing movement, mentation, and mood.* Neurol, 2004. **63**(6): p. 968-74.
25. Kramer, P., *Listening to prozac*. 1997, London: Penguin Books.
26. Wolpe, P.R., *Treatment, enhancement, and the ethics of neurotherapeutics.* Brain Cogn, 2002. **50**(3): p. 387-95.
27. Zola, I., *Socio-medical inquiries*. 1983: Temple Univ. Press.
28. Conrad, P., *Medicalization and social control.* Annu Rev Sociol, 1992. **18**: p. 209-232.
29. American Psychiatric Association. *S 12 Mild neurocognitive disorder*. DSM-5 Development 2011 [cited 2011 June 10, 2011]; Available from: http://www.dsm5.org.
30. American Psychiatric Association, *Dementia of the Alzheimer's type*, in *Diagnostic and statistical manual of mental disorders (Revised 4th ed.)*. 2000, Author: Washington, DC.
31. Whitehouse, P.J. and E.T. Juengst, *Antiaging medicine and mild cognitive impairment: Practice and policy issues for geriatrics.* J Amn Geriatr Soc, 2005. **53**(8): p. 1417-1422.
32. Bond, J., *The medicalization of dementia.* Journal of Aging Studies, 1992. **6**(4): p. 397-403.
33. Bartus, R.T., et al., *The cholinergic hypothesis of geriatric memory dysfunction.* Science, 1982. **217**(4558): p. 408-14.
34. Steele, L.S. and R.H. Glazier, *Is donepezil effective for treating Alzheimer's disease?* Can Fam Physician, 1999. **45**: p. 917-9.
35. Pfizer Canada Inc., *Multinational study confirms positive effects of treatment with ARICEPT in patients with severe Alzheimer's disease*, in *CNW*. 2007.
36. NICE, *Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease: Review of NICE technology appraisal guidance 111*, in *NICE technology guidance 217*, Author, Editor. 2011: London.
37. Mckee, S., *Nice 'yes' for AD drugs to treat mild forms of the disease*, in *PharmaTimesOnline*. 2011: UK.
38. Alzheimer's Society, *Mild cognitive impairment*, N. Fox, Editor. 2010.
39. Birks, J. and L. Flicker, *Donepezil for mild cognitive impairment.* Cochrane database of systematic reviews, 2006. **3**: p. CD006104.
40. Belluck, P., *Guidelines allow earlier definition of Alzheimer's*, in *New York Times*. 2011.

41. Whitehouse, P.J., *Meanings and matters of early states of dementia*, in *The Eleventh International Congress*. 2003, International Psychogeriatric Association: Chicago, USA.
42. Repantis, D., et al., *Antidepressants for neuroenhancement in healthy individuals: A systematic review.* Poiesis Prax, 2008. Published online: 27 November 2008.
43. Greely, H., et al., *Towards responsible use of cognitive-enhancing drugs by the healthy.* Nature, 2008. **456**(7223): p. 702-5.
44. Maher, B., *Poll results: Look who's doping.* Nature, 2008. **452**(7188): p. 674-5.
45. Sahakian, B. and S. Morein-Zamir, *Professor's little helper.* Nature, 2007. **450**(7173): p. 1157-9.
46. McCabe, S.E., et al., *Non-medical use of prescription stimulants among US college students: Prevalence and correlates from a national survey.* Addiction, 2005. **100**(1): p. 96-106.
47. Wilens, T.E., et al., *Misuse and diversion of stimulants prescribes for ADHD: A systematic review of the literature.* J Am Acad ChildAdolesc Psychiatry, 2008. **47**(1): p. 21-31.
48. Repantis, D., et al., *Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review.* Pharmacol Res, 2010. **62**(3): p. 187-206.
49. Outram, S.M., *The use of methylphenidate among students: The future of enhancement?* J Med Ethics, 2010. **36**(4): p. 198-202.
50. Mehta, M.A., et al., *Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain.* J Neurosci, 2000. **20**(6): p. RC65.
51. Schermer, M., et al., *The Future of psychopharmacological enhancement: Expectations and policies.* Neureothics, 2009. **2**: p. 75-87.
52. Larriviere, D. and M.A. Williams, *Neuroenhancement: Wisdom of the masses or "false phronesis"?* Clin Pharmacol Ther, 2010. **88**(4): p. 459-461.
53. British Medical Association, *Boosting your brainpower: Ethical aspects of cognitive enhancement*. 2007, British Medical Association: London, UK.
54. Commission de l'éthique de la science et la technologie, *Position statement on psychotropic drugs and expanded uses: An ethical perspective*. 2009: Québec.
55. Larriviere, D., et al., *Responding to requests from adult patients for neuroenhancements: Guidance of the Ethics, Law and Humanities Committee.* Neurol, 2009. **73**(17): p. 1406-12.
56. Nelkin, D., *Selling science: How the press covers science and technology*. Revised edition ed. 1995, New York: W.H. Freeman and Company.
57. Kitcher, P., *Science, truth, and democracy*. 2001, New York: Oxford University Press.
58. Brown, N., *Hope against hype- accountability in biopasts, presents and futures.* Sci Stud, 2003. **16**(2): p. 3-21.
59. Rose, S.P.R., *How to (or not to) communicate science.* Biochem Soc Trans, 2003. **31**(part 2): p. 307-312.
60. Racine, E., et al., *Contemporary neuroscience in the media.* Soc Sci Med, 2010. **71**(4): p. 725-33.
61. Gray, A.J., *Stigma in psychiatry.* J R Soc Med, 2002. **95**(2): p. 72-76.

62. Illes, J., et al., *Neurotalk: Improving the communication of neuroscience research.* Nature reviews. Neuroscience, 2010. **11**(1): p. 61-9.
63. Racine, E., O. Bar-Ilan, and J. Illes, *Brain imaging: A decade of coverage in the print media.* Sci Commun, 2006. **28**(1): p. 122-142.
64. Diefenbach, G., et al., *Portrayal of lobotomy in the popular press: 1935-1960.* J Hist Neurosci, 1999. **8**(1): p. 60-9.
65. Racine, E., et al., *"Currents of hope": Neurostimulation techniques in U.S. and U.K. print media.* Camb Q Healthc Ethics, 2007. **16**(3): p. 312-6.
66. Bell, E., G. Mathieu, and E. Racine, *Preparing the ethical future of deep brain stimulation.* Surg Neurol, 2009.
67. Racine, E., et al., *Media coverage of the persistent vegetative state and end-of-life decision-making.* Neurol, 2008. **71**(13): p. 1027-1032.
68. Racine, E. and C. Forlini, *Cognitive enhancement, lifestyle choice or misuse of prescription drugs? Ethics blind spots in current debates.* Neuroethics 2008.
69. Riis, J., J.P. Simmons, and G.P. Goodwin, *Preferences for enhancement pharmaceuticals: The reluctance to enhance fundamental traits.* J Consum Res, 2008. **35**(3): p. 495-508.
70. Williams, S.J., et al., *Waking up to sleepiness: Modafinil, the media and the pharmaceuticalisation of everyday/night life.* Sociol Health Illn, 2008. **30**(6): p. 839-55.
71. Bubela, T.M. and T. Caulfield, *Do the print media "hype" genetic research? A comparison of newspaper stories and peer-reviewed research papers.* CMAJ, 2004. **170 9**(9): p. 1399-1407.
72. Forlini, C., *The cognitive enhancement trifecta*, pers comm, 2009: Montreal.
73. Forlini, C. and E. Racine, *Autonomy and coercion in academic "cognitive enhancement" using Methylphenidate: Perspectives of a pragmatic study of key stakeholders.* Neuroethics, 2009. **2**(3): p. 163-177.
74. Forlini, C. and E. Racine, *Stakeholder perspectives and reactions to "academic" cognitive enhancement: Unsuspected meaning of ambivalence and analogies.* Public Understanding of Science, 2010. December 5: p. 1-20.
75. Coveney, C.M., B. Nerlich, and P. Martin, *Modafinil in the media: Metaphors, medicalisation and the body.* Soc Sci Med, 2008. **68**(3): p. 487-495.
76. Connemann, B.J., et al., *Donepezil and flight simulator performance: Effects on retention of complex skills.* Neurol, 2003. **61**(5): p. 721-22.
77. Singh, I. and K.J. Kelleher, *Neuroenhancement in young people: Proposal for research, policy, and clinical management.* AJOB Neurosci, 2010. **1**(1): p. 3-16.
78. Appel, J.M., *When the boss turns pusher: A proposal for employee protections in the age of cosmetic neurology.* J Med Ethics, 2008. **34**(8): p. 616-8.
79. Warren, O.J., et al., *The neurocognitive enhancement of surgeons: An ethical perspective.* J Surg Res, 2009. **152**(1): p. 167-172.
80. Dow Jones. *Factiva*. 2011 [cited 2011 June 11]; Available from: http://www.dowjones.com/factiva/.
81. Racine, E., D. DuRousseau, and J. Illes, *From the bench to headlines: Ethical issues in performance-enhancing technologies.* Technol, 2007. **11**: p. 37-54.
82. Forman, J. and L. Damschroder, *Qualitative content analysis.* Adv Bioeth, 2008. **11**(9): p. 39-63.

83. Neuendorf, K.A., *The content analysis guidebook*. 2002, Thousand Oaks, CA: Sage Publications.
84. Racine, E., et al., *Hyped biomedical science or uncritical reporting? Press coverage of genomics (1992-2001) in Québec.* Soc Sci Med, 2006. **62**(5): p. 1278-1290.
85. Shin, S.-J. and O. Lemon, *Diagrams*, in *The Stanford Encyclopedia of Philosophy (Winter 2008 Edition)*, E.N. Zalta, Editor. 2008.
86. Copi, I.M., *Introduction to logic*. 1982, New York: Macmillan Publiching Co., Inc.
87. Silvers, A., *A fatal attraction to normalizing: Treating disabilities as deviations from "species-typical" functioning,* in *Enhancing Human Traits: Ethical and Social Implications*, E. Parens, Editor. 1998, Georgetown University Press: Washington.
88. McMahan, J., *Cognitive disability and cognitive enhancement*, in *Cognitive Disability and Its Challenge to Moral Philosophy*, E.F. Kittay and L. Carlson, Editors. 2010, Wiley-Blackwell: West Sussex.
89. Berry-Kravis, E., et al., *A pilot open label, single dose trial of fenobam in adults with fragile X syndrome.* J Med Gen, 2009. **46**(4): p. 266-71.
90. Healy, A., R. Rush, and T. Ocain, *Fragile X syndrome: An update on developing treatment modalities.* ACS Chem Neurosci, 2011.Article ASAP.
91. Wallis, C., *Fragile X: Unraveling autism's secrets*, in *Time Magazine*. 2008.
92. Hecht, F., *Fragile X gene.* Science, 1991. **253**(5027): p. 1467.
93. Roberts, L., *Report card on the genome project.* Science, 1991. **253**(5018): p. 376.
94. Annas, G.J., *Questing for grails: Duplicity, betrayal and self-deception in postmodern medical research.* J Contemp Health Law Policy, 1996. **12**(2): p. 297-324.
95. Roberts, L., *The human genome. Controversial from the start.* Science, 2001. **291**(5507): p. 1182-8.
96. Kuehn, B.M., *Scientists find promising therapies for fragile X and Down syndromes.* JAMA, 2011. **305**(4): p. 344-6.
97. Hagerman, R.J., et al., *Advances in the treatment of fragile X syndrome.* Pediatrics, 2009. **123**(1): p. 378-390.
98. Harris, G., *Promise seen in drug for retardation syndrome*, in *New York Times*. 2010.
99. Healy, M., *Hope builds for treating intellectual disabilities,* in *Los Angeles Times*. 2011.
100. *A case for cautious optimism.* Nat Neurosci, 2010. **13**(6): p. 651.
101. Martin, L., *Approaches towards modeling neurodevelopmental disorders in animals*, B.C. ART-NeuroDevNet Winter Institute Lecture, Editor. 2011: Banff.
102. Elliott, C., *A philisophical disease: Bioethics, culture and identity*. 1999, New York: Routledge.
103. Mehlman, M.J., et al., *Ethical and legal issues in enhancement research on human subjects.* Camb Q Healthc Ethics, 2011. **20**(1): p. 30-45.
104. Tufts-New England Medical Center Evidence-based Practice Center, *Criteria for determining disability in infants and children: Short stature*: Summary. US Department of Health and Human Services, 2003.

105. American Psychiatric Association. *A 00 Intellectual developmental disorder*. DSM-5 Development 2011 [cited 2011 June 8]; Available from: http://www.dsm5.org.
106. American Psychiatric Association, *Mental retardation*, in *Diagnostic and statistical manual of mental disorders (Revised 4th edition)*. 2000, Author: Washington, DC.
107. Kevles, D.J., *In the name of eugenics: Genetics and the uses of human heredity*. 1985, New York: Knopf.
108. Lippman, A., *Led (astray) by genetic maps: The cartography of the human genome and health care.* SocSci Med, 1992. **35**(12): p. 1469-1476.
109. Lippman, A., *Prenatal genetic testing and screening: Constructing needs and reinforcing inequities.* Am J Law Med, 1991. **17**(1/2): p. 15.
110. Davich, J., *Chicago family come to grips with genetic disorder: Fragile x syndrome runs rampant in local family*, in *Chicago Parent*. 2011.
111. Chelala, C., *Drug offers hope for the mentally disabled*, in *The Japan Times*. 2010.
112. Berube, M., *Equality, freedom, and/or justice for all: A response to Martha Nussbaum*, in *Cognitive Disability and Its Challenge to Moral Philosophy*, E.F. Kittay and L. Carlson, Editors. 2010, Wiley-Blackwell: West Sussex.
113. Asch, A., *Prenatal diagnosis and selective abortion: A challenge to practice and policy.* Am J Public Health, 1999. **89**(11): p. 1649-57.
114. McDonough, P., *Congenital disability and medical research -- the development of amniocentesis.* Women Health, 1990. **16**(3): p. 137 - 153.
115. Schalock, R.L., *The concept of quality of life: what we know and do not know.* J Intellect Disabil Res. **48**(Pt 3): p. 203-16.
116. Special Olympics. *R-word: Spread the word to end the word*. 2011 [cited 2011 June 8]; Available from: http://www.r-word.org/.
117. The Canadian Down Syndrome Society. *About the Canadian Down syndrome society*. [cited 2011 June 8]; Available from: http://www.cdss.ca/about-the-canadian-down-syndrome-society.html.
118. Fenton, A. and T. Krahn, *Autism, neurodiversity and equality beyond the 'normal'*. 2009, DigitalCommons@McMaster.
119. Sacks, O., *An anthropologist on mars*. 1995, New York: Vintage.
120. Barnbaum, D.R., *The ethics of autism: Among them, but not of them*. 2008, Bloomington: Indiana University Press.
121. Fragile X Research Foundation of Canada. *Home*. 2009 [cited 2011 June 8]; Available from: http://www.fragilexcanada.ca/.
122. Bolt, L.L., *True to oneself? Broad and narrow ideas on authenticity in the enhancement debate.* Theor Med Bioeth, 2007. **28**(4): p. 285-300.
123. Little, M.O., *Cosmetic surgery, suspect norms, and the ethics of complicity*, in *Enhancing Human Traits: Ethical and Social Implications*, E. Parens, Editor. 1998, Georgetown University Press: Washington.

APPENDICES

Appendix 2-1: Print media sample.

Unknown. (2002). Briefs: New clues in Alzheimer's. The Record.

Unknown. (2002). Drug found to improve performance among pilots. Airline Industry Information.

Unknown. (2002). NEW Memory pill- In brief. The Times.

Unknown. (2002). New potential for Alzheimer's and cholesterolemia markets. Medical Marketing & Media.

Unknown. (2005). A clever idea? The drugs that made you smart. Irish Independent.

Unknown. (2009). A stimulating debate. Irish Independent.

Arnst, C. (2003). "I can't remember"; Drugs to stave off age-induced memory impairment may be on the horizon. Business Week.

Balfour, N. (2002). Superbrain future, recycled water, better oxygen supply, Alzheimer drug boost for healthy memory. The Sunday.

Bee, P. (2007). Smart drugs for straight A's. The Times.

Begley, S. (2004). New ethical minefield: Drugs to boost memory and sharpen attention. The Wall Street Journal.

Burne, J. (2007). Can taking a pill make you brainy? Daily Mail.

Evenson, B. (2002). Alzheimer's drug improves 'working memory': Side effects possible: Older pilots remember training better in test. National Post.

Gibson, E. (2008). Mental pick-me-ups: "Cognition drugs" such as Adderall and Provigil are fast gaining popularity--despite health and ethics issues. Business Week.

Healy, M. (2005). Call these drugs IQ-profen/ Brain research is leading to quick advances toward 'smart pills'. Los Angeles Times.

Healy, M. (2005). Newest drugs act as brain's fountain of youth. The Grand Rapids Press.

Jaffe, S. (2002). Scientists test theories on aging and their resolve: Researchers become case studies for their own work. The Plain Dealer.

Kher, U. (2006). Can you find concentration in a bottle? Time (Canadian Edition).

Laurence, J. (2005). Messing with our minds. The Independent.

Laurence, J. (2009). Mind-Enhancing drugs: Are they a no-brainer? The Independent.

Macintyre, B. (2004). Extreme makeover for the brain. The Times.

McCook, A. (2002). Alzheimer's drug ups memory in healthy pilots. Reuters Health E-Line.

Miller, H. and D. Longtin (2004). Smart pill, anyone? The Washington Times.

Morgan, J. (2008). Brain-boosting drugs could soon become the smart choice. The Herald Final.

O'Neil, J. (2002). Testing medicine and memory. The New York Times.

Reucroft, S. and J. Swain (2002). Smart drug. The Boston Globe.

Rosenthal, R. (2009). Data needed on cognition-enhancing drugs. Pediatric News.

Stuttaford, T. (2002). Memory drug has landed-Medical briefing. The Times.

Appendix 2-2: Interdisciplinary bioethics literature sample.

Bolt, L. L. (2007). "True to oneself? Broad and narrow ideas on authenticity in the enhancement debate." Theoretical medicine and bioethics 28(4): 285-300.

Bush, S. S. (2006). "Neurocognitive enhancement: ethical considerations for an emerging subspecialty." Applied neuropsychology 13(2): 125-136.

Chatterjee, A. (2004). "Cosmetic neurology: the controversy over enhancing movement, mentation, and mood." Neurology 63(6): 968-974.

Chatterjee, A. (2006). "The promise and predicament of cosmetic neurology." Journal of Medical Ethics 32(2): 110-113.

Chatterjee, A. (2007). "Cosmetic neurology and cosmetic surgery: parallels, predictions, and challenges." Cambridge quarterly of healthcare ethics : CQ : the international journal of healthcare ethics committees 16(2): 129-137.

Cheshire, W. (2008). "The pharmacologically enhanced physician." American Medical Association Journal of Ethics 10(9): 594-598.

Choudhury, S., S. K. Nagel, et al. (2009). "Critical neuroscience: Linking neuroscience and society through critical practice." Biosocieties 4(1): 61-77.

de Jongh, R., I. Bolt, et al. (2008). "Botox for the brain: enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories." Neuroscience and Biobehavioral Reviews 32(4): 760-776.

Douglas, T. (2008). "Moral enhancement." Journal of applied philosophy 25(3): 228-245.

Farah, M. J., J. Illes, et al. (2004). "Neurocognitive enhancement: what can we do and what should we do?" Nature reviews Neuroscience 5(5): 421-425.

Forlini, C. (2008). "Examining discourses on the ethics and public understanding of cognitive enhancement with methylphenidate."M.A. en bioéthique, Université de Montréal.

Gerlai, R. (2003). "Memory enhancement: the progress and our fears." Genes Brain and Behavior 2(4): 187-190.

Lanni, C., S. C. Lenzken, et al. (2008). "Cognition enhancers between treating and doping the mind." Pharmacological Research 57(3): 196-213.

Larriviere, D., M. A. Williams, et al. (2009). "Responding to requests from adult patients for neuroenhancements: Guidance of the Ethics, Law and Humanities Committee." Neurology 73(17): 1406-1412.

Mehlman, M. J. (2004). "Cognition-enhancing drugs." The Milbank quarterly 82(3):483-506.

Mehlman, M. J. and J. W. Berg (2008). "Human subjects protections in biomedical enhancement research: Assessing risk and benefit and obtaining informed consent." The Journal of law, medicine & ethics : A journal of the American Society of Law, Medicine & Ethics 36(3): 546-549.

Normann, C. and M. Berger (2008). "Neuroenhancement: status quo and perspectives." European archives of psychiatry and clinical neuroscience 258 Suppl 5: 110-114.

Racine, E. and J. Illes (2006). "Neuroethical responsibilities." The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques 33(3): 269-277, 260-268.

Riis, J., J. P. Simmons, et al. (2008). "Preferences for enhancement pharmaceuticals: The reluctance to enhance fundamental traits." Journal of Consumer Research 35(3): 495-508.

Vincent, J. A. (2007). "Science and imagery in the 'war on old age'." Ageing & Society 27: 941-961.

Warren, O. J., D. R. Leff, et al. (2009). "The neurocognitive enhancement of surgeons: An ethical perspective." Journal of Surgical Research 152(1): 167-172.

Whitehouse, P. J. (2004). "Paying attention to acetylcholine: The key to wisdom and quality of life?" Acetylcholine in the Cerebral Cortex 145: 311-317.

Appendix 2-3: Coding structure used to analyze headlines of media articles and titles of bioethics articles that provided coverage of both the cognitive enhancement debate and the DFSS.

*Section 1: Media headlines**
1.1. Enhancement claimed
Enhancement property
Pharmaceutical use
Context of enhancement
Current
Anticipated
Questioning
1.2. Other themes conveyed
Property affected
Medical use
Pharmaceutical use
Questioning

* *Section 2: Bioethics titles* used the same coding structure.

Appendix 2-4: Coding structure used to analyze colloquialisms that explicitly refer to donepezil within media and bioethics articles that provided coverage of both the cognitive enhancement debate and the DFSS.

*Section 1: Media colloquialisms**
1.1. Cognitive enhancement
1.2. "Smarts"
1.3. Memory enhancement
1.4. Other

* *Section 2: Bioethics colloquialisms* used the same coding structure.

Appendix 2-5: Coding structure used to analyze the DFSS and the media and bioethics articles that provided coverage of both the cognitive enhancement debate and the DFSS.

*Section 1: Media coverage of the DFSS**

1.1. General study information
- Author's name or affiliation
- Published in _____ journal
- Date of publication

1.2. Study Characteristics
- Purpose statements
- Sample size and subject information
- Tests, tasks, and dosage information
- Time-frame of the study
- Control information

1.3. Results or findings of the study
- Extended results
- Specific results
- Qualifying clauses
  - Practical
  - Epistemic

* *Section 2: Bioethics coverage of the DFSS* used the same coding structure;
Section 3: Information provided within the DFSS used the same coding structure.