Prescribing Drugs for Cognitive Enhancement

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Introduction

Cognitive enhancement or “neuroenhancement”, has been defined as “the use by healthy individuals of medical technologies to augment cognitive abilities” [1]. These medical technologies range from prescription medications to transcranial magnetic stimulation or even invasive techniques such as gene therapy and deep brain stimulation [2]. For the purpose of this review, we will concentrate on enhancement by medications which are readily available for prescription; stimulants in the amphetamine and methylphenidate classes, modafinil and beta blockers.

History and Current Usage

The desire to improve our cognition beyond the natural is not a modern invention. Rene Descartes was an early advocate for cognitive enhancement, stating in the 1600s that “if it is possible to find some means that generally render men more wise and more capable ... I believe we must seek for it in medicine” [3]. Even earlier in history the ancient Greeks used rosemary twigs in their hair to improve memory [4] and many cultures have herbal remedies specific to improving thinking or memory [5].

Today the proliferation of “energy drinks” and other caffeinated products [6] promising improved wakefulness suggest a continued comfort with altering our cognition through artificial means. Who among us has not relied on coffee or caffeine during times of little sleep and looming deadlines [7]? Among students this comfort now appears to extend into prescription medications, especially stimulants used to treat attention-deficit/hyperactivity disorder (ADHD) [8]. One survey of American colleges reported a mean rate of off-label stimulants use of 6.9% with ranges from zero to as high as 25% [8]; although some may be for recreational purposes [9]. Elsewhere, off-label stimulant use has been reported in up to 16% of Italian university students [10] and 0.78 to 1.55% of similar populations in Germany [11]. Although the prescribing of stimulants has clearly increased in the past 20 years [8], it remains unclear whether off-label use is actually increasing [12]. Data on other enhancing medications is scant and it remains unclear who uses them and how often. A 2008 survey of Nature readers did show that 20% of 1400 responders had used methylphenidate (MPH), modafinil or beta-blockers, with usage rates reported as 62%, 44% and 15% respectively [13].

These studies highlight the use of cognitive enhancers in academic populations. However, a recent survey of American physicians suggests the practice may be more widespread: 67% of respondents reported receiving requests for enhancing medications at least monthly and 12% daily [14]. If the desire for cognitive enhancement is indeed this prevalent, then physicians need a practical approach to successfully navigate such requests in an efficient and ethical manner.

Cognitive Enhancing Medications: Evidence for use

Stimulants

Stimulants such as MPH and dextroamphetamine (d-AMP) are widely reported in the media as promoting concentration and attention [15] and polled university students report similar reasons for their use [16]. Scientific evidence for this effect, however, is lacking: a recent systematic review and meta-analysis of blinded placebo controlled trials of MPH use for cognitive enhancement did not show any significant effect on attention [19]. The same analysis did report positive effects on visuospatial working memory and many of the included studies showed subjective increases in attention and alertness. Interestingly, not all effects were positive; one study showed increased impulsivity and task specific error rate with MPH use [17].
Similar data exists for d-AMP and mixed amphetamine salts. A 2011 systematic review on the use of amphetamine compounds in healthy adults concluded that these drugs “appear to enhance retention of recently learned information and, in at least some individuals, also enhance working memory and cognitive control” [20]. However, the authors cautioned that the results varied significantly across the included studies with many showing no significant effect over placebo. An earlier systematic review concluded that d-AMP (and MPH) “may actually impair performance on tasks that require adaptation, flexibility and planning” [21]. Furthermore, single studies have suggested that individuals with better baseline cognitive function or specific genotypic differences may actually do worse on cognitive tests when taking d-AMP [22,23,24].

It is plausible that the popularity of stimulants may at least in part be due to their perceived safety [18]. Post marketing surveillance and trial data on stimulant use in adult patients with ADHD shows that such medications are generally well tolerated [16,19,25], although there is lack of long-term follow-up [25]. The most common reported adverse effects amongst all users included abdominal pain, anorexia and insomnia with small increases in heart rate and blood pressure seen in adults [16]. Of note is the Federal Drug Administration ‘black box’ label warning regarding abuse potential as well as risks of psychosis and affective disorders. The risk of psychosis appears to be low with appropriate dosing [25] but the potential for abuse is important to consider when prescribing for enhancement purposes. One survey of university students reported 43% of off-label stimulant use was to “provide a high”. Among students with ADHD in this survey, 54% had been approached by others “to sell, trade or give away their medication” [26]. Not surprisingly, illicit use, for any purpose, of stimulants was associated with higher rates of drug and alcohol abuse [26].

**Modafinil**

Modafinil is a wakefulness promoting agent approved for the treatment of narcolepsy as well as excessive day-time sleepiness in sleep apnea and shift-work sleep disorder [19]. Its mechanism of action is unclear but appears to differ from stimulants such as MPH and, as a result, modafinil is believed to have a lower potential for abuse and addiction [27]. Its current use as a cognitive enhancer seems to be primarily in increasing alertness in jet-lagged or sleep-deprived individuals [19,13,28]. Nonetheless, a meta-analysis of the evidence for its use in non-sleep deprived individuals suggests a moderate positive effect on attention. Single studies have also reported limited benefits in some specific neuropsychological tests assessing attention, short-term memory, response times and task error rates [29-33]. Among sleep deprived individuals, the effects seem more robust with significant improvements in executive function, memory and wakefulness [19]. Interestingly, a retrospective analysis found that the effects on cognition in non-sleep deprived adults were only among the subgroup with a lower IQ [34].

As with stimulants, modafinil appears to be well tolerated both in short-term use as a cognitive enhancer [19] and from available clinical trial data in narcolepsy and other disorders causing excessive daytime sleepiness [27]. Common side-effects included headache, dizziness, nausea, rhinitis, pharyngitis, dry mouth, anorexia, nervousness [27] and insomnia in non-sleep deprived individuals [19].

**Beta-Blockers**

Beta-blockers often go unmentioned in the cognitive enhancement debate as they do not appear to improve cognition [35]. Their use is mainly for combating performance anxiety, commonly in public speaking or among musicians. Nonetheless, this can also be considered a form of enhancement as performance anxiety is not a medically recognized disorder [36]. Beta-blocker use, mainly propranolol, is widely reported among studies involving musicians [37-39] with unclear rates of use in the general population. Systematic reviews of non-randomized trials of propranolol or nadolol, another beta-
blocker, have shown decreased anxiety in musical performance [37,38] with single studies showing improvements in performance quality [40]. Additionally, one blinded placebo controlled trial in surgical residents showed a decrease in surgical tremor and anxiety [41].

Data from the above reviews and the migraine literature suggests that beta-blockers are generally well tolerated [37,38,43], even in the higher doses used for migraine prophylaxis. The most common reported side-effects included exercise intolerance and fatigue with measured decreases in heart rate and blood pressure when used chronically in migraine patients [42].

**Ethical Issues**

The major arguments for and against the practice of prescribing cognitive enhancers can be framed according to the commonly accepted principles of medical bioethics: respect for autonomy, beneficence, non-maleficence and justice [43]. These will be briefly reviewed here.

**Justice**

The principle of justice can be broadly summarized as “fair, equitable, and appropriate treatment in light of what is due or owed to persons” [43]. Many authors have raised concerns that access to cognitive enhancing medications will, at the very least initially, be unfairly limited to wealthier patients who can afford the drugs and may be more knowledgeable of their existence [2,4,44,45,49]. This is often countered by the fact that many such advantages already exist: access to good nutrition, computers and private tutors can all improve our cognitive or academic performance [2,44]. Furthermore, some data suggests that cognitive enhancing medications have less or even no effect in those with higher IQs [34]. It is unlikely, therefore, that currently existing medications will create any great inequality as they lack the efficacy to improve us beyond the limits already established by nature [2].

Other distributive arguments hinge on the use of physicians as a resource for these prescriptions. Traditionally, some have defined the physician role narrowly as “to heal the sick, not turn healthy people into gods” [46]. Others argue that if the definition of health is taken as “a state of complete physical, mental and social well-being” [47], then any intervention which improves patient well-being could conceivably be considered part of the physician role [48]. Precedents for enhancing treatments already exist; cosmetic surgery and hair-loss remedies can all be considered treatments which enhance well-being rather than treating disease [2,49]. This does however, lead to the question of whether requests for cognitive enhancement medications should be covered as an insured health service. Given the similarity between cognitive enhancement and other enhancing treatments one could argue that this should be paid for out of pocket.

Additional concerns arise regarding the potential for occupational or academic coercion with cognitive enhancers. Already there are media reports of military pilots being encouraged to take amphetamines for long flights or risk being grounded [50]. In the medical field, a study has shown that modafinil improves cognitive performance in emergency physicians working night shifts [51]. Could similar evidence be eventually used to insist that emergency physicians take modafinil on night shifts in the name of patient safety? Will students be compelled to take stimulants to earn acceptance into highly ranked schools? The answers likely hinge on the perceived risks but are concerning in the context of pathologizing normal human fatigue or attention [45].
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Autonomy
Autonomy has been defined as a respect for persons and an obligation to promote their free choices [43]. When a competent patient who is well informed of the risks and benefits asks for a cognitive enhancing medication, what right does a physician have to refuse a prescription? This question can be addressed on two fronts: as mentioned earlier, many consider enhancing medications to fall outside the traditional goals of medicine [49]. As a result, physicians have no ethical obligation to comply with such requests [36], similar to the right to deny requests for treatments which are considered to fall outside the standard of care. Secondly, because these medications affect our cognition and may have potential for addiction [50], it is conceivable that the process of informed consent may be influenced by coercion from underlying drug dependence or personality changes induced by the medications [49].

Beneficence and Non-Maleficence
Physicians have a general duty to act in the best interests of the patient and to avoid or minimize harm [43]. Prescribing a cognitive enhancing medication may be viewed as improving well-being through improved performance at work or in the academic setting. However, it is important to keep in mind that the evidence for the efficacy of current cognitive enhancers is actually quite minimal. While evidence does exist for some improvement in the controlled setting of clinical studies, it remains unclear whether or how this translates into real world performance [29,53].

Reassuringly, the risk of harm associated with these drugs appears to be minimal. Nonetheless, prescribing physicians must exercise caution due to lack of data on long-term use of cognitive enhancing medications. Significant abuse potential also exists, possibly even for modafinil [50]. Physicians must also be aware that single studies reported negative cognitive effects with cognitive enhancing medications [17,54] suggesting that gains in some areas of cognition may be offset by losses in other domains [2].

Approaching Requests for Cognitive Enhancing Drugs
Irrespective of the existing evidence, patients are still likely to ask for prescriptions for cognitive enhancers, especially given the positive effects portrayed in the media [15]. Below we present an approach to dealing with such requests in a primary care setting.

1. Explore the reason for the request and screen for medical causes of the patient’s complaint
What concerns about performance and/or cognition does the patient have? Are their concerns a change from baseline? Is there an underlying undiagnosed medical or neurological disorder? There is no evidence regarding the incidence of undiagnosed cognitive disorders in patients requesting cognitive enhancement. Intuitively, screening for medical causes of cognitive impairment, depression, ADHD, dementia or shift work sleep disorder may be appropriate depending on the clinical context.

2. Consider conservative measures
What else has the patient tried for their cognitive complaints? How is their sleep and nutrition? How do they study? Non-medical measures may be appropriate and sufficient in some cases, avoiding the risks associated with cognitive enhancing medications. Measures will vary but can include education regarding sleep habits, counselling about study methods and stress management techniques. For performance anxiety, enrollment in a public speaking clubs or courses may be helpful and there is clinical trial evidence for benefits with cognitive behavioural therapy [38].
3. **Inform the patient of the risks and benefits and establish therapeutic goals**
What are the patient’s goals in requesting a cognitive enhancer? Are they aware of the potential risks? Exaggeration of the effects of drugs such as MPH in the media is relatively common [15] and as such, patients may have unrealistic expectations. Physicians must clarify that this is ‘off-label’ usage, explain that the benefits are uncertain and likely minimal and identify known and potentially unknown risks [49]. Given the uncertain benefit, it would be reasonable to have a much lower risk threshold than when prescribing the medications for therapeutic purposes [2]. Pre-established therapeutic goals will serve to curb unrealistic expectations[49] and provide a window for drug discontinuation in the future.

4. **Consider short-term trials**
Given the dearth of long-term safety information for many cognitive enhancing medications, short-term trials may represent a risk management strategy until more evidence for safety is available. For example, prescribing a stimulant for one week during final exams may be a more reasonable option than providing a prescription for the entire academic year.

5. **Consider objective measures of drug effect**
As with any medication used off-label, the possibility of a subjective response with no objective improvement must be considered. Measures such as a change in grades or job performance evaluations may be considered as a metric for possible medication benefit. Due to potential for abuse or dependence, it may be helpful to involve a family member or friend in conversations regarding benefit and appropriate use[49].

6. **If prescribing a stimulant, choose a drug with the lowest possibility of abuse**
Longer acting forms of stimulants (extended release MPH) appear to have lower risks of diversion or abuse than traditional forms of MPH [16, 18].

7. **Follow up frequently to assess efficacy and look for side-effects**
Frequent follow up is essential to ensure ongoing medication benefits that outweigh the risk of continued use. A low threshold for discontinuation is reasonable if benefits are unclear.

**Conclusion**

Requests for cognitive enhancement appear to be a relatively common and possibly increasing phenomenon, especially among university students. The evidence for cognitive benefits with currently available drugs is minimal. However, cognitive enhancing medications appear to be relatively low risk in short-term use, aside from the abuse potential of short acting stimulants. Physicians have no professional obligation to prescribe such medications to healthy patients but ethical considerations exist and should be taken into account when evaluating requests for cognitive enhancement. Each request must be assessed on an individual basis and screening for undiagnosed cognitive disorders is essential. If the decision to prescribe a cognitive enhancer is made, early establishment of therapeutic goals and education on actual evidence for risks and benefits is important. Using long acting forms of stimulants and short-term trials may help minimize risk of adverse effects.
References


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