



**Mental Capital and Wellbeing:
Making the most of ourselves in the 21st century**

**State-of-Science Review: SR-E9
Pharmacological Cognitive Enhancement**

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Summary

Improvement of various facets of cognition by pharmacological substances is now commonplace. Many pharmacological interventions are aimed at improving cognition in specific neuropsychiatric disorders where cognitive impairment is a prominent symptom, such as Attention-Deficit Hyperactivity Disorder (ADHD), schizophrenia, Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD). Enhanced cognition would, in turn, lead to improved functional outcome and quality of life. Importantly, pharmacological enhancement of cognition in both the young and old healthy populations seems set to become increasingly popular, extending from dietary supplements and caffeine to drugs specifically targeted at improving cognition.

The effects of pharmacological substances on cognition are complex, as cognition is a multi-faceted construct encompassing attention, executive functioning and spatial and verbal learning and memory. Most cognitive enhancing drugs improve only specific aspects of cognition such as forms of executive functions or memory, which are mediated by different systems in the brain. The sizes of the effects to date range from small to moderate, but as pointed out by a recent report by the Academy of Medical Sciences, even small percentage increments in performance can lead to significant improvements. While, the extension of enhancement from the controlled laboratory environment to daily life is controversial, several factors are contributing to the advent of increasingly effective approaches. These include the development of sophisticated neuropsychological tests, and the routine inclusion of multiple, converging behavioural and brain-imaging measures. With the development of human pharmacogenetics, uncovering human genetic polymorphisms relating to cognition, such as the catecholamine-O-methyltransferase (COMT) gene, cognitive enhancers may be matched to those that might benefit from them the most. Moreover, with the popularisation of the notion of cognitive enhancement, pharmacological interventions are being seen as a means not only to improve existing deficits, but also to prevent decline before its onset, and even to enhance normal functioning.

As pharmacological cognitive enhancement appears set to become increasingly widespread, the profile of cognitive effects of each drug on specific populations should be mapped, along with its potential for harms. This will facilitate ethical and regulatory discussion about each pharmacological substance. The development of tailored, cognitive enhancing treatments for a wide range of neuropsychiatric disorders, as well as for normal function, holds much future promise.

1. Introduction

Intact cognitive resources, encompassing attention, executive functions, learning and memory, are essential for everyday functionality and mental capital. This is apparent in the loss of functionality, mental capital and wellbeing resulting from impaired neurocognitive function in neurodegenerative and neuropsychiatric disorders. Pharmacological interventions can potentially ameliorate some aspects of cognitive dysfunction, thereby improving mental capital and consequently everyday function and quality of life. While the link between cognition and wellbeing in healthy individuals is less clearly established (Whalley and Deary, 2001), the popularity of substances such as caffeine in enhancing alertness, concentration and other aspects of cognition highlights the central role of cognition to functionality, even in healthy adults.

Pharmaceutical cognitive enhancers (PCE) have been, and are being, developed to address cognitive impairment in neurodegenerative and neuropsychiatric diseases where impaired cognition is core to the

disorder. In these cases, including Alzheimer's disease (AD) and Attention-Deficit Hyperactivity Disorder (ADHD), enhancing cognitive dysfunction is central to supporting the individual's mental capital.

With the development of increasingly effective drugs, cognitive impairment is being targeted for direct pharmaceutical treatment in other neuropsychiatric diseases where cognitive dysfunction is less prominent. For instance, increasing evidence indicates that cognitive dysfunction in schizophrenia is associated both with impaired functional and subjective outcomes (Morein-Zamir et al., 2007). Likewise, treatment of cognitive impairment in neurodegenerative disorders such as multiple sclerosis is increasingly being investigated in order to improve patients' mental capital (Christodoulou et al., 2006; Porcel and Montalban, 2006).

There is also evidence that PCEs authorised for patient populations are being used by healthy individuals, as in the case of stimulant medication for ADHD being taken by college students (White et al., 2006).

2. Understanding the neuropharmacology of cognition

In recent years, technological advances in understanding neurotransmitter systems at the cellular level, together with brain imaging techniques and the development of sophisticated computerised testing of cognitive functions, have all facilitated our understanding of the neurochemistry of cognition. While current research recognises the remarkable complexity of neurochemical function and its influence on behaviour, such advances enable the development of novel PCEs better targeted at specific cognitive systems. These advances will ultimately serve to sustain mental capital within, and across, individuals.

Current pharmacological influences on cognition are largely non-specific, in part due to the overlapping and complex interdependence of different cognitive processes. Thus, in many disorders, multiple cognitive domains are impaired, as with schizophrenia where executive functions and attention are disrupted along with learning, memory and perception (Heinrichs and Zakzanis, 1998).

Nevertheless, substantial progress has been made in differentiating cognitive functions and elucidating their respective underlying neurochemical and neural substrates. For example, we know that preserved executive functioning depends primarily on intact frontal lobes and fronto-striatal pathways, whereas episodic memory and learning depend to a larger degree on intact temporal lobes including the hippocampus.

Pharmacological intervention is further modulated by complex interactions between neurotransmitters, such as cortical interactions between noreadrenaline (NA) and dopamine (DA) (Arnsten, 2000). Likewise, the blockade of serotonin receptors leads to increased mesocortical dopamine (Apud and Weinberger, 2006) and the modulation of the impact of DA on executive function (Matrenza et al., 2004). Nevertheless, neurochemical specialisation is also apparent, with pharmacological double dissociations being found for cognitive functions (Chamberlain et al., 2006a).

With increasing understanding of the brain's neurochemistry using imaging techniques and animal models, the complex roles of pre-existing baseline levels, drug dosage and individual differences are becoming more apparent. The Yerkes-Dodson principle suggests that the relationship between optimal performance and neurotransmitter function is often that of an inverted U-shaped curve, with deviations from the optimal level in either direction impairing performance (Cools, 2006; Mehta and Riedel, 2006). For instance, low levels of noradrenaline engage α_2 receptors thereby improving executive function. However, at higher levels of noradrenaline, α_1 receptors also become engaged, which impairs prefrontal functionality (Ramos and Arnsten, 2007). A similar relationship is evidenced between DA and working memory function (Vijayraghavan et al., 2007).

Research has also revealed different neurotransmitter levels across brain regions, suggesting a complex interplay between baseline levels and drug administration. While some cognitive functions may improve following drug administration, others may worsen, as they depend on different optimum neurotransmitter levels (Cools et al., 2003). A detailed understanding of how enhancing one cognitive domain can, on occasion, come at the expense of another (Academy of Medical Sciences, 2008) will allow for explicit, information-based decision-making in treatment options.

These findings strongly suggest that drug-induced neurotransmitter increases may improve functioning in some groups but impair performance in others, already at optimum. It is not uncommon for PCEs to improve performance primarily or exclusively in individuals with greater impairment (e.g. Mehta et al., 2000). However, there is also evidence demonstrating that healthy volunteers can also improve performance with the cognition-enhancing drugs methylphenidate (Elliott et al., 1997) and modafinil (Turner et al., 2003a).

2.1. Better specificity

The field of pharmacogenomics has begun to unravel the role of particular genetic variations in individual differences in drug responsiveness, though to date single genes generally account only for a small percentage of the population variance (Diaz-Asper et al., 2006). For example, the val158met COMT gene has been linked to the degree of effectiveness of COMT inhibitors and to working memory performance (Apud et al., 2007). Likewise, the therapeutic response in AD appears to be genotype-specific, with APOE-4/4 carriers as the worst responders to conventional treatments (Cacabelos, 2005). Thus, developments in pharmacogenomics will make it possible to anticipate individual responsiveness and to target particular subgroups for effective PCE with greater efficacy and reduced side-effects.

While many drugs influence one or more neurochemical systems throughout the brain, increasingly specific compounds are being developed. This is important as research has demonstrated that many neurochemicals are involved in multiple functions. For example, DA in the pre-frontal cortex (PFC) modulates cognitive functioning, while DA involvement in addiction and motivated behaviour is mediated largely by subcortical systems. Currently, the emphasis is on developing compounds that selectively increase DA in the PFC, but not subcortical areas, in order to enhance cognitive functioning with a reduced likelihood of drug dependence (Apud and Weinberger, 2006). Hence, while amphetamine has extensive effects on DA throughout the brain, tolcapone primarily modulates DA levels in the PFC by acting as a COMT enzyme inhibitor (Zurcher et al., 1990), which removes DA and is present mostly in the PFC (Apud and Weinberger, 2006). Such highly-specific drugs would allow for the augmentation of cognition in the domains most needed, again with minimal side effects.

With the rapid advancements being made in understanding the underlying neurochemical and neurocognitive systems of mental function, the brain's complexity is being harnessed to influence cognition in increasingly sophisticated and targeted ways. Thus, multiple levels or methods can be used to achieve the same goal or similar goals, such as increasing DA levels in PFC by inhibition of COMT or by blockade of NA reuptake sites.

3. Neuropsychiatric and neurological disorders

Treatment of neuropsychiatric and neurological disorders by psychopharmacological means is commonplace, allowing for increased mental capital, functionality and independence. Two main domains of cognition in which PCEs have a marked influence are memory and learning, and executive functioning including attentional processing.

3.1. Memory and learning

Efficient use of learned information and effective learning of new knowledge and skills are key to our ability to adapt to the ever-changing demands and constraints of modern daily life. Learning facilitates the augmentation of one's cognitive reserve (Barnett et al., 2006). To date, memory and learning have been partitioned into several functions mediated by different brain areas, including episodic, semantic and procedural memory. Episodic memory, one of the most cardinal types, conveys factual learning and memories of past events and is largely mediated by the hippocampus and related temporal lobe structures. Cellular processes likely to be involved in learning and memory formation are *long-term potentiation* (LTP), which is a use-dependent increase in synaptic strength (Martin et al., 2000; Rose et al., 2005), and *neurogenesis*, with the birth of new hippocampal neurons being linked to memory formation (Gould et al., 1999; Shors et al., 2002).

Research into PCE of memory and learning has largely been instigated by the increasing population suffering from dementia and its associated personal and financial costs (de Rover et al., 2008). Loss of cholinergic projections is a classic feature of dementia, and AD patients experience marked reductions of cortical nicotinic acetylcholine receptors (Kadir et al., 2006). In accordance with the prominent role of acetylcholine in memory formation and its impairment in dementia, treatment has focused largely on enhancing neural transmission in the cholinergic system.

Cholinesterase inhibitors, the most common drugs used for treating dementia, inhibit the breakdown of acetylcholine by blocking acetylcholinesterase and are considered the first line of defence for improving cognition and functionality to a moderate degree (Hansen et al., 2007; Lee et al., 2007a; Rozzini et al., 2007; Seltzer, 2007). Protective effects of some cholinesterase inhibitors have been suggested as they may also reduce toxic amyloid-beta peptide (Ballard et al., 2007). Nevertheless, the long-term efficacy of such drugs is still being debated (Hansen et al., 2007; Seltzer, 2007).

Likewise, nicotine and related drugs, which stimulate acetylcholine receptors, have been proposed to treat dementia. Though acute or temporary administration of nicotine in animal models and AD patients has produced evidence of cognitive enhancement (Buccafusco et al., 2005; Marti Barros et al., 2004; Newhouse et al., 2001; Sahakian et al., 1989), long-term enhancement after chronic nicotine treatment still remains to be demonstrated for AD (Lopez-Arrieta et al., 2000).

Given the central role of glutamate in cognition and memory in particular, drugs are also being developed that target AMPA or NMDA receptors. For example, memantine partially blocks NMDA receptors hypothesised to be overactive in AD, with recent studies suggesting its effectiveness in combination with acetylcholinesterase inhibitors (Weycker et al., 2007; Winblad et al., 2007), though see also Doggrell (2003) and Ferris (2003). Such research suggests the utility of a polypharmaceutical approach, as multiple neurotransmitters are affected.

Methods are also under development to target downstream processes including second messenger systems such as cyclic adenosine monophosphate, together with, for instance, phosphodiesterases inhibitors (Rose et al., 2005). Likewise, ampakines, which bind to AMPA receptors and enhance synaptic response, accelerate long-term memory encoding (Lynch and Gall, 2006). Ampakines appear to be of particular value to age-related memory impairments (Lynch, 2002; 2004) but they also enhance some aspects of memory in young adults (Ingvar et al., 1997).

Neurotrophic drugs are also under development (Bae et al., 2000; Ruether et al., 2001), but research into their efficacy on cognitive performance and daily living remains to be carried out (Wei et al., 2007).

Memory impairments are also present in neuropsychiatric diseases such as schizophrenia, playing a role in impeding functionality (Green, 1996). Accordingly, cholinesterase inhibitors have been proposed as add-on treatments to antipsychotic medication in patients with cognitive deficits (Risch et al., 2007), though see (Chouinard et al., 2007a; 2007b; Lee et al., 2007b). Moreover, impairments in the nicotinic receptor mechanism have been uncovered so, consequently, $\alpha 7$ nicotinic receptor agonists such as MEM 3454 have been proposed as treatment candidates (Martin and Freedman, 2007). As PCEs in schizophrenia are still in their infancy, there is insufficient data regarding their effectiveness in increasing mental capital and wellbeing.

Although episodic memory is by far the most studied, there are also many recent advances in basic research on other forms of memory. Memory, particularly emotional memory, can also be enhanced by NA (Chamberlain et al., 2006c). The understanding that excessive NA release and $\alpha 1$ adrenergic receptor engagement are likely to play a role in the instigation of post traumatic stress disorder has led to relatively successful attempts at $\alpha 1$ receptor blockade in patients (Raskind et al., 2007; Taylor et al., 2006). Furthermore, clonidine, an NA $\alpha 2$ receptor agonist, has been shown to improve memory and attention in groups such as patients with Korsakoff's amnesia (Mair and McEntee, 1986), schizophrenia (Fields et al., 1988) and PD (Riekkinen and Riekkinen, 1999). However, clonidine can also impair working memory in acute studies in healthy adults (Chamberlain et al., 2006b).

In sum, while the need for memory improvement and disease retarding treatments for dementia are the driving force for developing episodic memory-related PCEs, basic research suggests multiple methods for enhancing different memory systems.

3.2. *Executive functioning and attention*

Intact executive functioning appears key to rewarding social interactions, sound decision-making, and an adaptive response style that allows us to avoid impulsive and inappropriate behaviours. All of these are essential for mental capital and wellbeing. Executive functions encompass numerous domains of mental processing and include working memory, cognitive flexibility, planning and inhibition of inappropriate actions (Norman and Shallice, 1986; Robbins, 2007).

These functions are largely mediated by the PFC and fronto-striatal 'loops', and are modulated by many neurotransmitters, including glutamate, GABA and the monoamines (DA, NA and serotonin) (Arnsten and Robbins, 2002). For instance, optimal DA levels appear critical for working memory performance, whereby information is actively stored and manipulated in the absence of external stimulation (Goldman-Rakic, 1995; 1996). Attentional processing encompasses the ability to concentrate over time and to focus selectively while ignoring distracting information. While NA regulates attention, arousal and vigilance (Aston-Jones and Cohen, 2005; Smith and Nutt, 1996), various components of related processing are also influenced by dopamine and serotonin (Robbins, 2005). Thus, there appear to be many potential avenues for targeting executive and attentional dysfunction.

Catecholamine dysfunction in the PFC commonly impairs executive functioning and attentional performance in neuropsychiatric disorders including ADHD, schizophrenia and depression. Stimulants such as amphetamines and methylphenidate which affect cognitive function by increasing extracellular DA and NA are the medication of choice for ADHD (Solanto, 1998). Methylphenidate has been found to improve working memory, cognitive flexibility, attention and response inhibition in adults and children with ADHD (e.g. Aron et al., 2003; Scheres et al., 2003; Turner et al., 2005). However, it may also impair some aspects of performance in healthy adults (Elliott et al., 1997). Additional dopaminergic medications can assist in some cognitive aspects but impair others, as evidenced in Parkinson's Disease (Cools et al., 2003; Swinson et al., 2000). The functional significance of this has yet to be ascertained. As noted previously, DA involvement in additional functions such as motor control and addiction lead to some dopaminergic medications having

unwanted side-effects. Consequently, different approaches are being employed, targeting DA indirectly or targeting related neurochemicals. For example, the potential for abuse of stimulants is being addressed by new administrations designed for slow release (Jones et al., 2005).

Increasingly, drugs targeting primarily the NA system are being seen as viable treatments to some aspects of executive dysfunction. Atomoxetine, a selective NA reuptake inhibitor, has recently been licensed for ADHD and is believed to exert its influence by increasing the levels of NA and DA in the PFC but not the striatum (Stahl, 2003). Although the cognitive effects of atomoxetine have yet to be extensively examined, preliminary evidence suggests it is associated with improved selective attention and response inhibition, but not spatial working memory (Chamberlain et al., 2007; Faraone et al., 2005). Likewise, guanfacine, a NA α 2A agonist, has been shown to improve attentional and executive functioning in ADHD (Scahill et al., 1999; 2001).

Many executive function difficulties in schizophrenia are related to decreased connectivity and abnormal activity in the PFC (Walterfang et al., 2006). An effective approach would be a targeted, possibly genotype-based, pharmacology treatment (Apud and Weinberger, 2006). Numerous potential drugs have been proposed, including atomoxetine and D1 agonists under development, as well as modafinil (Turner et al., 2003a), which at present is at the clinical trials stage (Morein-Zamir et al., 2007).

PFC hypoactivation has also been linked to cognitive impairment in depression (Chamberlain and Sahakian, 2006). In fact, many drugs developed as anti-depressants, such as selective serotonin reuptake inhibitors (SSRIs) also directly improve cognition, though differences in their dopaminergic and noradrenergic activity result in distinct cognitive profiles that have yet to be surveyed (Jones et al., 2005). Preliminary evidence suggests that additional groups of people may benefit from executive function PCEs including stroke patients, such as those suffering from hemispatial neglect, and individuals experiencing cognitive impairment following traumatic brain injury (Mehta and Riedel, 2006; Salmond et al., 2005; Tenovuo, 2006).

Although this review has focused separately on each cognitive domain, there is a degree of interdependence among them. For example, cholinesterase inhibitors, believed to target primarily long-term memory processing, can enhance attentional processing and working memory function, potentially through improved encoding of the information (Barch, 2004).

4. Cognitive enhancement in the healthy population

To date, pharmaceutical cognitive enhancement has mainly been deployed to improve the substantial cognitive impairment resulting from brain injury and neuropsychiatric disorders. This is, in part, due to existing regulations. Current trends include broadening the application of already licensed drugs to additional conditions (e.g. cholinesterase inhibitors developed for AD used in schizophrenia (Stip et al., 2005); modafinil originally approved for sleep disorders now applied to shift workers and sufferers of excessive daytime sleepiness).

But change is in the air. The application of PCEs to the general population is now increasingly being discussed, as the effects of some cognitive-enhancing drugs may be suitable for healthy individuals, for example modafinil (Turner et al., 2003a). The daily demands of contemporary life which increasingly moves towards a 24/7 society often entail fatigue, jet lag and even temporary sleep deprivation, along with continuous stress. Such factors impair a wide range of cognitive functions including attention, executive functions, learning and memory (Sapolsky, 1998). The use of PCEs could increase mental capital in healthy individuals by promoting them to overcome such stressors. Even mild uncontrollable stressors can impair working memory functioning (Arnsten, 2000) and PCEs are increasingly being viewed as a viable means of coping with daily stressors.

Already, stimulant use in students is evident in North America (National Institute on Drug Abuse, 2007). In England, prescription rates of stimulants have almost doubled in the past decade (Postnote, Parliamentary Office of Science and Technology, 2007). Stimulants are used to improve concentration and alertness so students use them to study longer and perform better during exams. In spite of some cognitive enhancing abilities (Barch, 2004; Elliott et al., 1997; Mehta et al., 2000), stimulants may also have deleterious cognitive effects, a potential for abuse and even psychosis, thus precluding them from being considered good cognitive enhancers. Presently, effective PCEs with less potential for abuse are appearing on the market, such as modafinil which can enhance attention and some aspects of executive functions in both sleep-deprived individuals as well as normal young adults (Turner et al., 2003a).

The healthy, ageing population is also increasingly being considered as potential candidates for PCEs. Deficits in both executive functions and memory are among the most prominent problems with normal ageing (Rabbitt and Lowe, 2000). Neurochemically, the ageing brain demonstrates consistent abnormalities including the loss of naturally occurring catecholamine (Ramos and Arnsten, 2007). Psychophysical and neuropsychological evidence suggests that the cognitive decline stems from poorer signal-to-noise and down-regulated neuromodulatory function in older brains (Mahncke et al., 2006). In aged animals, noreadrenaline $\alpha 2$ agonists have beneficial effects on working memory (Arnsten and Goldman-Rakic, 1985), particularly under distracting conditions (Ramos and Arnsten, 2007). While several drugs are being investigated for treatment of memory impairments resulting from ageing, including ampakines (Lynch and Gall, 2006), several PCEs including methylphenidate have shown a relative lack of effect on working memory and sustained attention (Turner et al., 2003b).

5. Present and future of cognitive enhancers

The efficacy and safety of long-term administration of PCEs is continuously being investigated for licensed drugs. Yet there is a severe dearth of research into the ecological validity and long-term consequences of administering PCEs for promoting mental capital and wellbeing (Gorwood, 2006). Therefore, valid and standardised measurements for monitoring everyday function and wellbeing are essential (Duka et al., 2007). There are indications that, in at least some cases, cognitive enhancing effects can be transient (e.g. Lanctot et al., 2003, on cholinesterase inhibitors in AD).

Off-label use of PCEs in healthy adults, as in the healthy elderly population, and their effectiveness and long-term safety remain to be investigated. At present, there is only scant data about off-label use, largely restricted to stimulants in students (Babcock and Byrne, 2000; White et al., 2006). PCE use in healthy children must, especially, be informed by safety considerations, as the effects on the developing brain are not well understood. Likewise, the effects of drug-drug interactions on cognition are largely unknown (e.g. Bentue-Ferrer et al., 2003). This may become more central with neuropsychiatric and neurological patients being prescribed PCEs in addition to current treatments (e.g. along with antipsychotic medication for schizophrenia).

Given the complexity of psychiatric disorders, combined treatment encompassing medication and additional therapeutic techniques such as cognitive behavioural therapy are viable and have been proposed as more comprehensive than either treatment alone (e.g. for ADHD: Majewicz-Hefley and Carlson, 2007; Ward, 2007). Complementary effects suggest that PCEs can be used to support learning and the implementation of coping strategies (Barkley, 2006), which in turn can promote reduced medication dosages. The cost-effectiveness of such treatments is presently undecided (e.g. in AD, the effect of medication combined with neurocognitive activation via training (Barnett et al., 2006)).

While individual responses to PCEs vary considerably, research is elucidating factors predicting individual variations. Pharmacogenomics enables a more targeted approach, even though the interactions between

genes are largely unknown at present. As the particular mechanisms by which drugs influence cognition (e.g. modafinil, atomoxetine, ampakines) become better understood, they can be applied more effectively and better predictions made about those likely to benefit.

Despite what, on occasion, may be gathered from the popular press (Butcher, 2003), PCE effects on healthy individuals are, to date, generally modest and in many patients the effects are small to moderate. Nevertheless, even small percentage increments in performance can lead to significant improvements in function outcome (Academy of Medical Sciences working group report, 2008, p150). Some people do use PCEs regularly to compete in the work and study environments (Farah et al., 2004; Maher, 2008). Only future research will determine whether ongoing regimes of PCE can indeed enhance mental capital.

Those already close to their optimal performance are less likely to benefit from PCEs but may benefit in the face of temporary stressors including sleep deprivation and jetlag. At present, the social norms and attitudes for taking PCEs are not clearly understood, though they are likely to play a role in seeking and complying with pharmaceutical treatment (Sahakian and Morein-Zamir, 2007). Factors such as socioeconomic status and ethnic background may also in part determine attitudes towards neuropsychiatric medication and PCE use (e.g. Givens et al., 2007; McLeod et al., 2007).

Method of administration (e.g. drink versus pill form) also can influence social norms (e.g. caffeine). Globalisation is also influencing off-label use of PCEs via internet advertising and marketing. Despite the difficulties, monitoring and publication of off-label use of PCEs is essential for ascertaining general population-wide trends. There is evidence that many healthy individuals do not use PCEs regularly, but only when they feel circumstances require it (Maher, 2008), though cost may also play a role.

Ensuring that the public is informed and educated about current and future trends in cognitive enhancement is of paramount importance. Hence, the fact that most effects to date are moderate and limited in scope, as well as the relative potential for abuse and side-effects of the various drugs, should be advertised. Likewise, information regarding the evidence-based benefits of different drugs should be made easily available (e.g. via websites). Additional information could convey that some drugs may be more effective for particular subpopulations, as determined genetically or empirically, and whether long-term use or intermixing of 'smart' drugs would synergise efficiency or produce harmful effects.

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