



**FORESIGHT**

Drugs Futures 2025?

Perspective of the  
pharmaceutical industry

OFFICE OF SCIENCE AND TECHNOLOGY

While the Office of Science and Technology commissioned this report, the views are those of the authors, are independent of Government and do not constitute government policy.

# Contents

<b>Executive summary</b>	<b>1</b>
<b>1 Introduction</b>	<b>4</b>
1.1 The current state of the industry	4
1.2 Psychoactive substances for medical use – drivers and influences	7
1.3 Psychoactive substances for non-medical use – drivers and influences	10
<b>2 The survey results</b>	<b>12</b>
2.1 The questions	12
2.2 What new prevention/treatments for addiction and problem use may be developed?	12
2.3 What is the likelihood of new treatments for the management of pain?	16
2.4 What is the likelihood for the development of new drugs for mental health?	18
2.5 What is the likelihood of the development of new descriptions or definitions of mood disorders?	21
2.6 What is the likelihood of the development of specific drugs that are targeted to paediatric or geriatric care?	22
2.7 Cultural, ethical, legal, societal, business or regulatory changes required to allow development of new drugs for medical purposes	23
2.8 What psychoactive substances could be developed specifically for non-medical purposes?	25
2.9 Are there any other key broad issues not covered elsewhere?	27
<b>References</b>	<b>28</b>
<b>Appendix 1: Acknowledgements</b>	<b>30</b>
<b>Appendix 2: Survey material</b>	<b>31</b>
<b>List of publications: Drugs Futures 2025?</b>	<b>39</b>



# Executive Summary

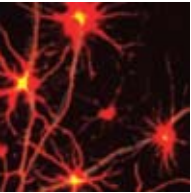
The Foresight project on Brain Science, Addiction and Drugs asked Dr Ian Ragan of CIR Consulting Ltd to find out the views of the pharmaceutical industry on the use of psychoactive substances in the future.

A questionnaire was sent to 16 pharmaceutical and biotechnology companies soliciting their views on the types of psychoactive substance that could be discovered within the next 20 years, and the changes to societal attitudes and business practices that would be needed to make these drugs available to patients and the general public. Of the 16 companies approached, nine responded.

The industry is cautious about the commercial viability of treatments specifically aimed at addiction, and has mixed views on the role that vaccines could play in its prevention. The industry is also much concerned about the ethics of preventative treatments. Nevertheless, there is optimism that drugs to enhance executive function, decrease impulsivity, and reduce stress and craving will be discovered anyway, whether specifically aimed at addiction or not. These could form part of a treatment regimen that combines the identification of at-risk groups, pharmacological and psychological treatments to reduce craving and prevent relapse, while simultaneously addressing co-morbid conditions.

Optimism about new treatments for neuropathic, inflammatory and functional pain is being driven by a better understanding of central sensitisation mechanisms and the role of inflammatory factors, as well as by confidence in drugs now in their early stages of development. However, the barrier to success is high because of concerns about safety, the poor predictive value of animal models, the lack of surrogate markers and abuse potential. In particular, there was no consensus among the industry respondents as to whether new treatments would be free from potential abuse.

In the area of mental health, the industry is optimistic that new treatments for depression and anxiety will be available in 5–10 years' time, showing that companies are already researching in these areas. Drugs for cognitive enhancement are seen as more challenging, because of difficulties with predictive animal models and with clinical trials. In schizophrenia, advances



in the near future will be in new adjunct therapies to support the atypical antipsychotic drugs by enhancing efficacy and reducing side-effects. The prevention of schizophrenia is not inconceivable from the scientific point of view but will be very difficult and ethically challenging. Other areas where new treatments may become available are sleep disorder, attention deficit hyperactivity disorder, mood stabilisation and autism.

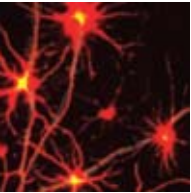
The industry believes that new diagnostic descriptions, definitions and subdivisions of mental illnesses will arrive within ten years, based perhaps on a better understanding of the pathophysiology and genetic basis of the disease, but more likely on treatment responsiveness. Lack of progress in this area could impede the proper understanding and use of genomic information in disease treatment. New drugs based on new definitions will follow with a 5–10 year lag.

In the area of treatments for specific age groups, the industry believes that paediatric medicine is especially difficult. Extrapolating from the adult what will happen in the child or adolescent is problematic, and therefore giving psychoactive substances to the developing brain brings real concerns about efficacy and long-term safety. The recent publicity over the use of antidepressants in adolescents will cast a shadow over the field for a long time to come. In geriatric medicine, there is more optimism and more investment. There is huge unmet medical need in Alzheimer's Disease, Parkinson's Disease, depression and sleep disorder among the elderly.

The industry is united in believing that greater transparency is essential over the societal changes needed to allow some of these scientific possibilities to reach the public. The industry will have a major role in providing information on how drugs will be used in the next few years and will make efforts to restore its tarnished image through early and open publication of clinical trial data. The industry hopes that its efforts will be reciprocated by increased understanding from the public and greater appreciation of risk and benefit from the regulators. The dangers are the trend towards increased post-launch monitoring and that of greater risk-averseness stifling innovation.

The industry is unanimous in its lack of enthusiasm for developing drugs for non-medical purposes. Most found the idea ethically indefensible in the current climate. Even if society changed to make it more acceptable, the industry's concerns about the risk and benefit of medicines where the benefit is medically marginal and where there is potential abuse or misuse remain a considerable obstacle. Therefore, the view is that non-medical uses will only arise off-label from drugs developed for real medical conditions, although the boundary between medical and non-medical is likely to change over the coming years. The areas in which this could happen are sleep, mood, stress, anxiety, impulsivity and vigilance.

The industry regrets what it perceives as an inadequacy of the national strategy for mental health, which it feels puts the UK at a disadvantage compared with the US. Many respondents reiterated that the proper treatment of mental illness could never be purely pharmacological. The future lies in better prevention, diagnosis and screening, the identification of at-risk groups, tailored pharmacological intervention, and counselling and psychological support. The industry no longer believes in magic bullets for mental illnesses.



# 1. Introduction

## 1.1 The current state of the industry

In predicting future developments in psychoactive substances, there is a great disparity between what is theoretically possible and what the pharmaceutical industry would consider pursuing. This involves more than estimating the probability that theoretical ideas might be realised or that there would be appropriate reimbursement for new substances. The industry is concerned about the ethical issues that have to be addressed when considering the future for the pharmacological manipulation of mood and cognition. An appreciation of the complexity of the question requires an understanding of the current state of the industry and the internal debate about the future shape of the business.

The current woes of the pharmaceutical industry are the subject of much attention these days.<sup>1-4</sup> It is apparent that the optimistic view of the 1980s and 1990s – that new technology would transform the business – has not yet been realised. The reasons include long lead times, higher-than-predicted levels of attrition in development of medicines and the lack of use of surrogates as regulatory endpoints for licensing. It is true that the way in which drug discovery is carried out has changed utterly, especially in the early phases where molecular biology has been astonishingly powerful in redefining the business. In addition, medicinal chemistry has been transformed by the development of automated synthesis and library generation, even if the initial enthusiasm for creating massive combinatorial libraries has waned. Armed with genome information, thousands of new drug targets and high-throughput methods, it is not surprising that the industry was bullish about the future. What has happened to dampen this enthusiasm?

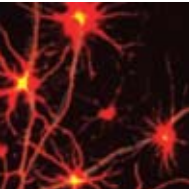
Many internal and external influences have led to the sector's present lack of confidence. The basic fact is that the rate of launch of new products has not matched the increased investment. Some analysts foresee a continuing decline in the number of new chemical entities receiving approval,<sup>5</sup> while others view the present state as a temporary blip which is already changing as the refocused efforts of the industry put new molecules into early clinical development.<sup>1</sup> However, there is no doubt that costs have increased



dramatically, while attrition rates have not reduced significantly along the value chain. Estimates put the cost of bringing a new molecule to the market at around \$1 billion.<sup>6</sup> The cost is spread across the entire chain from early screening to clinical trials because the lower costs per molecule at the early stage are cancelled out by their high failure rate. Drug discovery may be a complex and highly technical process but, it still relies heavily on trial and error. The effect of increasing cost is obvious – a greater return per launched product will be required. Even now, only one-third of launched drugs recoup their costs and are profitable for their discoverers. Small wonder, then, that the industry markets its successful products so aggressively and defends their patent exclusivity with such determination. This analysis therefore leads to another question – why has all this new science not led to a reduced attrition rate?

There are many possible answers of varying plausibility. The human genome has provided us with many thousands of potential drug targets, but not as many as we hoped for when we thought that the genome contained up to 100,000 genes. Estimates of the size of the subset of these that could be targets for effective small molecule therapies are obviously imprecise, but it is not likely to be more than a few per cent. The prospect of increasing the number of druggable targets by including biologicals (peptides, proteins and antibodies) will continue to be a rare or remote possibility for central nervous system (CNS) disorders. Therefore, the discovery that there may not be virtually limitless numbers of undiscovered drug targets has led to increased speculation that we may already have picked all the easy targets by traditional methods of discovery. If so, the remaining targets are going to be more challenging at the scientific level and the treatments are going to be less effective in the clinic. This could explain why attrition rates continue to be so high and why increased investment has not brought a corresponding return. The problem could be circumvented if methods of predicting drug efficacy at an early stage were more advanced. This applies especially in psychiatry and neurology, with higher attrition rates currently than in other therapeutic areas,<sup>7</sup> despite the possibility of better predictive tools such as PET and fMRI.

The failure of many plausible ideas to translate into effective therapies in the clinic, even with encouraging animal data, has already led to signs that some companies are beginning to re-assess the emphasis they put on CNS research, despite growing clinical need. The industry has to invest most heavily where it can succeed, and it does not have the luxury of responding only to medical need if the challenge of creating an effective medicine is too great.



The preceding argument has focused on factors that increase the cost of basic research. But the costs of clinical research have also risen dramatically. The number and complexity of studies required has grown, as has the individual cost per patient in the developed world. The number of trials and the number of patients enrolled into them has risen in response to the need for more data on both efficacy and safety. Competition between companies is much greater than it was, even ten years ago, and differentiating a new drug from competitor products is becoming more difficult. Thus, the need to have comparative studies to support marketing, formulary negotiations and reimbursement decisions has increased, and the recent spate of high-profile withdrawals, such as that of the pain killer Vioxx<sup>8</sup> continues to fuel the demand for more reassurance about safety in the context of the benefit that the medicine brings. The regulatory authorities increasingly mandate commitments to post-marketing studies as a condition for approval. Temporary pauses in clinical trials to address safety issues have trebled in the past few years compared with the late 1990s.<sup>2</sup>

At a time when the industry struggles with its ability to innovate, there is increasing downward pressure on the returns for innovation. Price regulation and cost containment measures are common throughout Europe<sup>1</sup> and it is likely that the same trends will occur in the US. The squeeze on the profits from existing drugs causes the industry to reflect on its portfolios and adopt a more conservative approach to its future investments in research and development. Already companies are investing very much less in blue-sky research than they were 15 years ago. This is not necessarily a bad thing if companies focus their minds on drug discovery and the academic sector is able to provide the basic science.

The collapse of the sales of the antidepressant, Prozac, after its patent life expired was a spectacular example of the power of the generics industry. The industry has to accept that the patent life of a product is the only period in which it can make money for its discoverers. Generic substitution also forces the realisation that in the future, mere incremental innovation will not lead to large sales, even if approval is gained. However, there is reason to hope that real innovation will continue to be rewarded, if the extension of data protection and market exclusivity for new indications remains. This will act as real encouragement.

One of the most obvious industry responses to these challenges has been merger and acquisition. The concept of merging two complementary entities, getting rid of the overlap and slimming the combined workforce is attractive from the business perspective and especially so for those who act as brokers in the process. In reality, the short-term effect is a loss of productivity and adverse effects on morale and the reputation of the industry.<sup>1</sup> In the long term, the loss of total research and development (R&D) is potentially

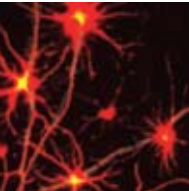
damaging. But reducing the competition may improve the chances that the survivors will succeed.<sup>1</sup> However, as a strategy, it has no long-term future because eventually the world will run out of companies to merge. When mergers do occur, assets are divested. Smaller companies can develop these with lower needs for a return. Such firms provide equity to the market themselves and build market capital, as well as collaborating with mainstream pharmaceutical companies. However, bigger companies are needed to develop these assets through to the market and make R&D affordable and sustainable in the long term. Likewise, the move of R&D to Asia, where costs are much lower, is helpful, but does not in itself address the underlying malaise of the industry.

Other responses such as focusing efforts on the core business, creating flexibility through outsourcing, and working in partnership with other stakeholders, hold out promise for a radical re-engineering of the way drug discovery and development are done, with the end goals of lower costs, faster development times and reduced attrition rates. Much of this depends on the success of new ideas in translational research and experimental medicine, and the promise of personalised treatment arising from the application of pharmacogenetics and pharmacogenomics.<sup>9,10</sup> Even then, the industry is nervous about the return on investment from such a radically changed business model. Success therefore depends as much on changes to the regulatory process as on basic science. The low esteem of the industry in the eyes of the world is a real impediment to a constructive dialogue on solutions to the industry's problems and on how to provide effective and much-needed medicines. The industry, battered by public opinion, is at risk of retreating into its shell at a time when working with other stakeholders is vital for medical progress.

In the context of possible future psychoactive substances, it is clear that the industry does not relish taking on all the scientific possibilities that might present themselves. The survey reveals that the industry is very aware of the ethical, legal and societal impacts of this kind of work and, while its reputation languishes at the same level as the tobacco industry, it is not surprising that there are areas into which the industry would not wish to stray when there are so many diseases for which treatments are genuinely needed.

## **1.2 Psychoactive substances for medical use – drivers and influences**

In the light of present concerns about the stability and future prospects of the business, this section looks at the positive drivers, influences and potential impediments to the development of new psychoactive substances for purely medical conditions. It concerns itself less with the scientific possibilities,



which need to be considered case by case, and more with general considerations of the pros and cons of investing in this field and the way in which medical treatments are likely to evolve as a result of societal changes.

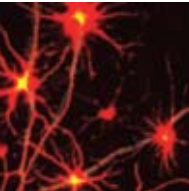
First and foremost, the driver for continued industry interest in this field is the huge unmet clinical need. This provides unlimited opportunities for novel breakthrough therapies and enormous market potential. The disease burden of CNS disorders is extraordinarily high<sup>11</sup> and even in areas of past success, such as depression, anxiety and schizophrenia, the proportion of patients receiving effective therapy is low, either because the treatment is ineffective, or because their problems have been undiagnosed or misdiagnosed, or because they have not received or taken effective treatment.

Western society at least expects to have effective treatments for mental health conditions that are increasingly accepted as real illnesses (but see below). However, there will be increasing pressure for drugs that affect the course of a disease rather than just relieving its symptoms. Other influences will be those already identified as necessary to transform the business model. For example, the heavily marketed blockbuster will give way to personalised medicine, while the belief in magic bullets for complex CNS disorders is already seen, in retrospect, as naive. Effective treatments will require combination therapies, polypharmacy and an individualised approach based on screening, early detection and monitoring.

The impediments to progress are formidable. The problem of attrition rates and increasing clinical trial burden is higher for CNS drugs than for others,<sup>7</sup> creating tension between unmet need and huge market potential on the one hand, and high risk of failure on the other. Companies may become risk-averse over both their science and their reputations. There is already suspicion that the industry invents diseases in order to sell cures, and that it actively promotes the medicalisation of normal life. An example that has attracted much publicity is attention deficit hyperactivity disorder (ADHD), regarded by some as society's failure to deal properly with the unusual behaviour of certain children. According to this viewpoint, drug companies have developed and marketed drugs for a condition that does not really exist and the availability of behaviour-modifying drugs masks the real need to address the underlying cause of the behaviour (e.g. see discussion in *Connecting Brains and Society*<sup>12</sup>). The truth is that ADHD is a real condition that can be controlled with drugs, but that pharmacology should be seen as part of a treatment regimen that must include appropriate attention to understanding the child's problems. To dismiss ADHD as a marketing department ploy is demeaning to all those who suffer from this condition. However, this example illustrates the extreme vulnerability of the industry to reputational damage if it is perceived to be taking advantage of societal ills to promote drug sales.

The issue is exacerbated by the inability to control the off-label use of a drug. At present, companies only develop drugs for *bona fide* medical conditions for which they conduct clinical trials. These conditions are those for which the drug is approved and which appear on the drug label. However, off-label use is both widespread and legal and can lead to a drug finding therapeutic and commercial success for conditions for which it was never designed (e.g. gabapentin<sup>13</sup> and modafinil<sup>14</sup>). This is beneficial under the right circumstances as it maximises the medical utility of the drug and recognises the fact that predicting therapeutic utility is still an imprecise science. In the absence of clinical trials of the new indication, however, the evidence for safety and efficacy can be said to be anecdotal, or at best uncontrolled. In the absence of robust evidence to confirm the efficacy and safety profile, there is a potential increased risk to patients and prescribers. Furthermore, there are other off-label uses ranging from the benign to the criminal that point up the dangers inherent in mood-altering drugs. At one end of this spectrum are the media stories about selective serotonin reuptake inhibitor (SSRI) antidepressants being used inappropriately by non-depressed people as pick-me-ups. They are unlikely to be effective as these drugs are not mood-altering *per se*. At the other end, there is the abuse of IV temazepam,<sup>15</sup> and even worse, the date-rape drugs, Rohypnol, gamma-hydroxybutyrate (GHB), ecstasy and ketamine.<sup>16</sup> It is inevitable that non-medical off-label use is going to occur with the kinds of new drugs envisaged in this survey, particularly if they are in general safer than earlier generations of medicines, as one would predict. There will be nervousness about the abuse potential of new mood-altering drugs, a problem that just does not arise in any other therapeutic area. It is an unfortunate fact that non-medical use of mood-altering drugs not only undermines the credibility of the companies who develop and market them, but also affects the patients who really need them.

Finally, there is the very complex and emotive issue of the safety of mood-altering drugs. New forms of substitute prescribing inevitably carry a risk of abuse. Perhaps the most widely debated issue among the public has been whether SSRI use is associated with increased risk of suicide. The debate continues, although there is no evidence that an increased risk exists in adults, despite the drugs' use in many millions of patients over many years. Recent regulatory reviews have confirmed that the risk–benefit ratio remains positive in all the licensed indications for SSRIs.<sup>17</sup> The future may provide the tools to screen out at-risk patients if rare but serious consequences turn out to have a genetic basis, but this is unknown. At present it seems logical to assume that any drug that alters brain chemistry will have the potential for causing thought disturbance in vulnerable people such as one might expect to find in a psychiatric population. The more successful the industry is in producing drugs with a more favourable risk–benefit ratio, the more likely it is that they will be used off-label for non-medical conditions.



### **1.3 Psychoactive substances for non-medical use – drivers and influences**

This section considers whether the industry would, or could undertake the *de novo* discovery and development of drugs purely for non-medical purposes. This is quite distinct from the off-label use referred to above. The issues that face the industry in providing a new generation of psychoactive substances for medical use are exaggerated many fold when non-medical use is considered. Some of these are scientific but many depend critically on public attitudes. It would be foolish to assume that these will remain fixed for the next 20 years.

Non-medical use should not be equated with recreational use. It is hard to imagine that the industry would set out to create a drug purely for mood alteration with all the dangers of abuse that would come with it. More plausible is the idea that the boundary between medical and non-medical use will shift as a result of greater societal acceptance of pharmacological intervention. According to a recent conference on the future of brain science,<sup>12</sup> voluntary use of drugs for non-medical purposes (including recreational use) does not seem to be a major societal issue. What concerns people more is the 'medicalisation of normalcy', with the implicit fear that redefinition of what is normal will bring with it some form of compulsion to treat perceived deviations from the norm.

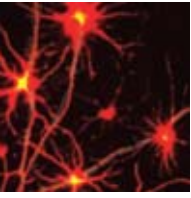
What are the non-medical non-recreational uses to which new psychoactive substances might be put? First, the control of 'abnormal' behaviour in normal settings, for example, aggression in schools, is already a topic of much current debate and concern. For those who do not accept that ADHD is a true disease, the custom in the US that children so diagnosed must be medicated in order to enter the school system is an example of what the future might hold.<sup>18</sup> Second, the enhancement of cognition to improve intellectual performance goes far beyond mere recreational use. Third, there is the use of drugs to normalise, or cope with responses to abnormal situations. Sleep deprivation and abnormal sleep patterns are a major cause of distress to the elderly, in which context it is a medical issue. However, large numbers of people enter professions voluntarily where sleep disturbance is an unavoidable consequence of the work e.g. shift-workers and airline crews. Such uses encourage fears of future civil control by pharmacological intervention, however unlikely this may be.

The driver for the industry actively to seek the development of such drugs is linked to what society finds acceptable. The market potential is obviously enormous. Who among us would not be tempted to use a safe, effective cognition enhancer if one were available? The trend to greater acceptability is already clear. Tinkering with Mother Nature, whether via botox, liposuction or drugs, is no longer veiled in secrecy. When the idea of designing drugs for

weight loss was first discussed, there were many voices in the industry who claimed that obesity was a lifestyle issue and that it was not the proper business of pharmaceutical companies. However, the view prevailed that pharmaceutical companies had no right to make moral judgements over a major cause of premature death. Furthermore, there is a lifestyle element to most major illnesses such as cardiovascular disease, cancer, arthritis and metabolic disorders. It is a much smaller step these days to the treatment of lifestyle alone than it was 15 years ago.

The impediments, though, are daunting and in essence are the same as for medical uses (Section 1.2) but more so. The safety aspects assume much greater importance for non-medical use. Although personalised medicine may help mitigate previously unforeseen and perhaps mechanistically unrelated side-effects, there is little doubt that the desired action of the drug will carry some risk for the user. When there is no disease to be treated, side-effects are clearly not tolerable, either from marketing, or ethical perspectives. The financial and reputational risks are off-putting.

There are also difficulties in the discovery and development of such drugs. Under the UK's 1986 Animal (Scientific Procedures) Act,<sup>19</sup> regulated procedures on protected animal species are only permitted where there are no scientifically suitable alternatives. In addition, the likely benefits (to man, other animals, or the environment) must be weighed against the likely welfare costs to the animals involved. Clearly, for non-medical uses, the benefit is harder to demonstrate. While the expansion of knowledge is also a legitimate justification for the use of animals in scientific procedures under UK law, it is difficult to see what reason there would be for causing pain, suffering or distress to animals in order to develop cognition enhancers for normal people, or to alleviate the stresses of modern lifestyle habits such as erratic working hours. In addition, regardless of the legal position, the sensitivity of the industry to its current poor image is likely to weigh heavily in any decisions. And from a purely scientific perspective, it is unclear what kind of animal models could be used to demonstrate efficacy for non-medical uses, and how clinical trials would be conducted.



## 2. The Survey Results

### 2.1 The questions

The intention was to ask the respondents what developments they thought possible over the next 20 years, but also to indicate the probability that these might occur within this timeframe and to add comments on their reasons. Section 1 of the survey focused on putative psychoactive substances for the treatment of addiction, pain, mental health and paediatric and geriatric care, topics that emerged as important from the Brain Science, Addiction and Drugs Project's scoping workshops. Section 2 asked questions about the ethical and regulatory aspects of drug development in the future and how these might help or hinder medical advances. Section 3 considered whether it would be possible to develop drugs specifically for non-medical purposes and, if so, in which areas. Finally, Section 4 asked for thoughts on topics not considered elsewhere, within the scope of the survey, where scientific advances could be used or stimulated to provide therapeutic advances. Nine companies listed in Appendix 1 contributed their ideas to the survey questions, which can be found in the online version of the report ([www.foresight.gov.uk](http://www.foresight.gov.uk)). A copy of the letter sent to companies inviting them to participate and a copy of the questionnaire used to collect data is in Appendix 2.

### 2.2 What new prevention/treatments for addiction and problem use may be developed?

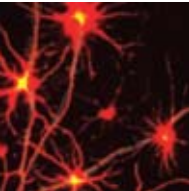
Addiction is now increasingly accepted as a complex disorder of the brain that has environmental, drug-related and genetic components.<sup>20</sup> It is defined as an intense compulsion to take a drug, over which the individual has impaired control, despite serious adverse consequences. The development of addiction requires chronic exposure to the drug whose initial acute effects typically activate brain pathways associated with positive reinforcement. The volitional phase of early drug use weakens as drug exposure leads to remodelling of brain pathways. This results in a complex set of behaviours that characterise addiction in which negative reinforcement plays an important part (tolerance, sensitisation, dependence, withdrawal, relapse sensitivity). This evolving pattern of addiction has led to distinction being drawn between drug addiction (associated with reward) and drug dependence (associated with withdrawal



symptoms) as the adaptive changes and triggers are different. This separation has practical applications as it provides treatment options aimed at reducing craving, ameliorating withdrawal, normalising behaviours and preventing relapse that involve many aspects of human brain function such as reward, motivation, learning, inhibitory control and executive function. This means that strategies need to address more than one aspect of addiction to be successful; pharmacology, psychology and social support need to work in partnership, and co-morbid conditions such as depression or schizophrenia need to be treated in parallel. As with all mental illnesses, complex disorders require complex and thoughtful intervention strategies. There are no magic bullets for addiction and never will be.

A further important aspect of drug addiction is the evidence that it is a developmental disorder. Normal adolescent characteristics, such as increased risk taking and sensitivity to peer pressure that make experimentation with drugs more likely, may reflect incomplete development of brain regions involved with executive function. But, in addition, it seems plausible that drugs taken at this developmental stage may have much greater propensity to remodel the brain than in adults. Certainly, exposure to alcohol and nicotine at an early stage results in greater vulnerability to addiction than later, adult exposure. This vulnerability is compounded by genetic factors, some of which have already been identified. However, polymorphisms in genes involved in the metabolism of drugs do not offer themselves as plausible targets for pharmacological intervention and, as yet, while there are interesting hints that polymorphisms in receptors in key reward pathways alter addiction vulnerability, translating such findings into effective therapies is not trivial. Finally, environmental factors play a major part in the development of addiction. Stress increases vulnerability to addiction and to relapse, while drugs of abuse cause abnormal responsiveness to stress. It is hardly surprising therefore that low socioeconomic class, low self-esteem and poor parenting go hand in hand with drug availability and abuse. Even in non-human primates, cocaine self-administration is linked to group status, with dominant animals showing less desire than those lower down the pecking order.

In their comments, the pharmaceutical company respondents covered a wide range of scientific and business issues that could have an impact on the development of new treatments. Improved identification of the genetic contribution to addiction could help through pharmacogenomics to identify treatment groups, even if such work did not lead easily to new molecular targets for therapy. On the other hand, progress with understanding the genes involved in alcohol addiction has identified some putative targets (e.g. gamma-aminobutyric acid type A (GABA-A) receptor subtypes) that are already under investigation for other CNS disorders. In this way, pharmacogenomic studies could provide the impetus to test novel drugs in addiction. Furthermore, since addictions resulting from various drugs of abuse



(e.g. opiates, cocaine, nicotine, alcohol) share some key features in common, it is likely that therapies aimed more downstream of the original site of action will generalise. An example is the use of opiate receptor antagonists such as naltrexone, for the treatment of both opiate addiction and alcoholism.

There are considerable difficulties that could impede progress to more effective therapy for addiction. The small size of the existing market, caused by the poor efficacy of current drugs, is a disincentive to entering the field as it would require an innovative approach to sales, marketing and distribution in order to create therapeutic and commercial success. Addicts frequently do not seek pharmacological treatment, and compliance is bad. One respondent proposed depot injections of drugs, as used in the treatment of schizophrenia, as a possible solution to this. Indeed, depot naltrexone is under evaluation at the current time. Physicians are often not proactive in making therapy available, and treatment centres, staffed largely by non-physicians, have the reputation of being anti-medication. Many countries do not provide reimbursement for the evaluation or treatment of drug abuse and addiction, which has discouraged the involvement of both the medical profession and the industry. There are also difficulties in conducting clinical trials. So it is not surprising that mainstream pharmaceutical companies have not shown a great appetite for this field in the past. However, effective partnership between the industry and government bodies concerned with health, the law and education could change the landscape greatly if society decided that this was a pressing enough need. There are already encouraging examples of success with Zyban (bupropion) and Subutex (buprenorphine).<sup>22</sup>

On specific treatments, the respondents were divided on the likelihood of vaccines for treatment and prevention. Opinion ranged from placing the possibility at quite high within five years to low even in ten years. Doubts were also expressed about the commercial viability of such products and the ethics of their use. A changed paradigm for drug development in this field could alter the financial picture, but some respondents found it difficult to imagine the circumstances in which a vaccine could be used preventatively. Addiction is not a communicable disease, although its propagation may have aspects of one. Therefore, concepts of social responsibility and herd immunity used to justify mass vaccination do not strictly apply. Furthermore, if the effect of the vaccine is to blunt or negate the rewarding properties of a drug, the risk is that the addict will simply self-administer higher doses. Such a strategy would only be successful where addicts are highly motivated to stop anyway, as in smoking. This group will inevitably have a choice whether or not to take the vaccine. However, there could be some instances where there might be consideration of the imposition of a vaccine, as with cocaine addicts who have been incarcerated because of drug-related crime, and for whom vaccination might be made a condition for early release from prison.

The ethical question of removing the choice of the addict to be treated is one that will have to be faced if and when such treatments become available. For nicotine and cocaine, this could be in five years. Vaccination technology could also be used to help prevent the initiation of the drug-taking habit. The most obvious target here is the adolescent. The ethical implications of giving a vaccine when it may neither be necessary, nor the choice of the recipient, again would need to be fully considered. There may be ways to help identify those most vulnerable, using a combination of environmental (e.g. lower socioeconomic group) and genetic factors. The former would no doubt bring accusations of class bias and stigmatisation, unless cocaine vaccination was imposed on the young urban professional class as well. The leading addiction vaccines in development at the moment are for nicotine and cocaine, but this list could be extended to other drugs of abuse, including heroin and phencyclidine (PCP) in the ten-year timeframe.

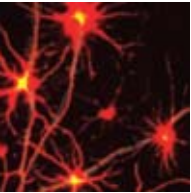
Drugs to enhance executive function were perceived as important and likely treatments. Different respondents expected them to become available in 5–20 years but added that they were unlikely to be specifically developed for the treatment of addiction.

Opinion on drugs to unlearn addiction was very mixed, ranging from never, to low probability even in 15 years, to moderate probability within five.

Better agreement was reached on the importance of anti-stress drugs, not only for relapse but also for drug seeking. Given the importance of this area for a wider variety of CNS disorders, all respondents predicted moderate to high probability of success in the 10–15 year timeframe or even less. One respondent foresaw a future in which the addict received in-patient treatment to become 'clean' and subsequently was put on a relapse prevention programme comprising both social aspects and the use of anti-craving drugs.

On one area, all correspondents were in accord. Combinations with psychological approaches were seen as absolutely inevitable in the next five years. Addiction will always need a combined approach. One respondent looking further ahead described the ideal future preventative treatment as one involving pharmacogenomics to identify the at-risk group, and then counselling and drug treatments to enhance executive function and decrease impulsivity.

Looking even further out, one respondent speculated about the use of imaging to identify brain regions associated with craving, with the patient able to use electrical stimulation of those regions to control desire. The success of deep brain stimulation in Parkinson's Disease and pain control clearly has potential in other conditions.



Some specific treatments were mentioned by a number of correspondents as being feasible in this 20-year timeframe. These included anti-craving drugs, drugs to improve compliance, drugs to ease withdrawal, specific treatments for alcoholism and the need for simultaneous treatment of psychiatric co-morbidities such as depression and schizophrenia. The list illustrates the wide range of options available for intervention in this complex area and the continuing need to consider multiple simultaneous approaches for effective therapy.

## **2.3 What is the likelihood of new treatments for the management of pain?**

To answer this question, it is important to define the kind of pain under consideration. There are four main categories of pain; nociceptive, inflammatory, neuropathic and functional.<sup>23</sup> The sensation of pain has strong cognitive and emotional components and is linked to autonomic function. All of these components contribute to the actual experience of pain. The perception of a painful stimulus relies on a specialised subset of nerves called nociceptors that relay signals to the brain via the spinal cord. As people are aware from those rare individuals who are genetically incapable of experiencing nociception, this form of pain is a very valuable warning and defensive system whose complete suppression by drugs is not desirable. If the nociceptive system fails to prevent tissue damage, the healing phase is promoted by inflammatory pain in the affected area, whose increased intensity serves to remind the individual to protect the tissue. Inflammatory pain should resolve as healing progresses. While this is a normal and positively beneficial process (so-called adaptive pain), it sometimes needs managing, for example, following surgery or traumatic injury or in abnormal states such as chronic inflammatory disease. The aim is to normalise pain responses, not to remove them entirely.

Other forms of pain are called maladaptive because they arise from abnormal sensory processing and are persistent or recurrent. The unmet need here is huge as treatment options are limited and understanding of the causes is at an early stage. Neuropathic pain arises from lesions of the peripheral nervous system caused by diseases such as diabetes, AIDS and post-herpetic neuralgia and from lesions of the central nervous system in such conditions as spinal cord injury, multiple sclerosis and stroke. Functional pain remains the least understood, as it is not associated with any deficit, lesion or abnormality. Functional pain conditions include fibromyalgia, irritable bowel syndrome and tension-type headache. Inflammatory, neuropathic and functional pain share the common feature of hypersensitivity in which normal innocuous stimuli become painful or mildly painful sensations become more severe. This sensitisation process has contributions from both the peripheral and central

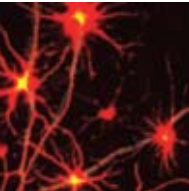
nervous systems and occurs at the level of the nociceptor terminals, the central ascending pathways to the brain and the descending inhibitory pathways, which offer a wide selection of plausible drug targets. Finally, not all forms of pain fit neatly into these categories. Migraine, for example, has both neurologic and inflammatory components. Cancer pain can be caused by inflammatory responses in affected tissues, and by nerve damage.

The prospects for future developments depend on the availability of plausible targets and the effectiveness of current treatments. In the treatment of nociceptive, inflammatory and neuropathic pain, there are efficacious treatment options currently available such as the opiates. Attention has focused on reducing side-effects, of which abuse potential is the most serious. Recent concerns about the safety and future prospects of the cyclo-oxygenase 2 (COX-2) inhibitors, Vioxx and Celebrex, have created a huge hole in treatment provision for inflammatory pain that will no doubt spur further efforts by the industry.

The respondents were in good agreement that new treatments would be available within five years, and ten at the most. This presumably reflects the fact that most major companies have active pain programmes that are in some stage of clinical development and would be expected to reach the market in this time. Most effort is directed to chronic neuropathic and inflammatory pain, as opiates are hard to beat in terms of efficacy in acute pain. The prospect of replacing them for non-scheduled treatments was considered unlikely.

This optimism was illustrated by one respondent who went into some detail about the increasing understanding of neuronal pathways and the influence of inflammatory signals. Insight into the central sensitisation mechanisms thought to be responsible for chronic spontaneous pain has provided several new molecular targets for drug discovery and development. Drug candidates for some of these that are already in early clinical trials could provide new treatments as early as 2010–2015. Other respondents supported the view that many new targets were also being pursued for neuropathic pain.

This optimism has to be tempered by concerns voiced by the same respondent and others that drugs for pain have to be very safe, as most conditions to be treated are not life-threatening. This is a serious hurdle to be overcome. In addition, the pain area has an unenviable record for the poor predictive value of animal models. Clinical development is hampered by the unavailability of surrogate markers of pain and therefore it is necessary to go to patients for the first indications of efficacy, something that the industry would prefer not to do. This can lead to competition for patients, which means delays in enrolment and completion of trials, and greater up-front costs before efficacy can be established.



Perhaps the most interesting disagreements were to be found in answer to the question about the development of drugs without abuse potential. The optimistic view was that most new targets have no theoretical abuse liability, presumably because they do not invoke opioid pathways, and therefore that the new drugs emerging in the 10–15 year timeframe would be free from this taint. Cymbalta (duloxetine) and Neurontin (gabapentin) were cited as examples of treatments already in use for neuropathic pain that apparently avoid this problem. However, the conservative view was that all drugs carry some risk of abuse, especially where reward is involved. In the case of pain, the reward is the removal of something unpleasant rather than the receipt of something pleasurable, but this means that any analgesic carries risk of abuse in patients, though not in the normal population.

## **2.4 What is the likelihood for the development of new drugs for mental health?**

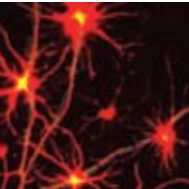
It is difficult to generalise across so broad a field. The detailed subquestions covered depression, anxiety, cognitive enhancement in schizophrenia, cognitive enhancement in neurodegenerative conditions, and prevention of schizophrenia. The field has been waiting a long time for a truly innovative breakthrough.

In depression, current treatments can trace their history back to the early fortuitous discoveries of iproniazid and imipramine that led to the formulation of the monoamine hypothesis of depression.<sup>24</sup> Since then, this has been the mainstay of efforts to develop new antidepressants. To search outside this zone of comfort is necessary but carries risk of failure. Excitement around neuropeptide targets has not abated totally, despite the disappointing failure of the neurokinin-1 (NK-1) antagonist, aprepitant (25), and this and other targets (e.g. corticotrophin releasing factor (CRF-1) receptor) continue to be proposed and developed as our knowledge of the pathophysiology of depression accumulates. The field was given an enormous jolt by the discovery that the previously noted promotion of neurogenesis by antidepressants was necessary for their behavioural effects.<sup>26</sup> This together with the evidence of stress-induced neuronal loss and its blocking by antidepressants has provided a whole new slant on depression and its treatment. Much work is going on in pharmacogenomics to trace common pathways, uncover new targets and determine disease and treatment susceptibility, but its impact on drug discovery is low at present. The field continues to debate the appropriateness of animal models of depression as opposed to behaviours responding to existing therapies, and this debate will continue until radically new ideas are tested in the clinic.

In anxiety, the story is much the same. Several companies have tried and are trying to develop second-generation anxiolytics based on subtypes of the GABA-A receptor that avoid the well-known side-effects of benzodiazepines. However, no new targets have yet provided anxiolytics that have been proven in the clinic.

The modest therapeutic success of the acetylcholinesterase inhibitors, donepezil, rivastigmine and galanthamine, has certainly encouraged the search for new and better cognition enhancers. The thinking behind such drugs was simply to replace a known deficiency, that is, to boost acetylcholine levels that had declined because of the loss of cholinergic neurones. There is probably a feeling that the acetylcholine deficiency in Alzheimer's Disease has already been dealt with as well as possible and the applicability of the concept to other cognitive disorders is limited. Therefore the field has moved on to consider other neurotransmitters such as glutamate,<sup>27</sup> or the downstream cyclic AMP response element binding protein (CREB) pathway.<sup>28</sup> Here the emphasis is less perhaps on restoring a simple neurochemical deficit and more on boosting existing systems and ultimately stimulating plasticity and brain repair. The latter thinking is behind the study of 'non-specific' cognitive enhancement in such conditions as stroke, hydrocephalus and acute brain injury. As in other areas of brain disease, the biological validation of new targets in animal models or tests remains problematical until these new ideas have been tested in the clinic. The appropriateness, or even feasibility of testing cognition enhancers in animals presents problems on two fronts. The first is how to choose a suitable deficit model in which to test drugs, particularly if the aim of the drug is not neurotransmitter replacement. The second bears on a later question in the survey over whether it is possible to develop cognition enhancers to augment normal function in man, and therefore whether it would be necessary to demonstrate efficacy in normal animals to justify development.

In the field of schizophrenia, the success of the atypical antipsychotics in providing some alleviation of most of the core symptoms of the disease has to be set against the fact that no one knows exactly why these drugs are effective.<sup>29</sup> The reason is simply that the most successful have very complex pharmacology and act at many different CNS receptors. The field has moved from believing that one of these receptors was responsible for all the positive benefits to the understanding that it is the mix of effects that brings therapeutic utility. Theories abound on which aspects of the pharmacology are related to the efficacy of these drugs and which to the side-effects. It is by no means clear that the two will separate cleanly anyway. Consequently, the industry struggles to identify plausible new approaches, and it recognises the extreme difficulty of reproducing or improving the mix of pharmacology present in successful drugs such as Zyprexa (olanzapine) and Clozaril (clozapine). Experience in this area has led to an increasing belief in the



industry that magic bullets based on single mechanisms of action do not exist for CNS disorders. Furthermore the call for 'magic shotguns',<sup>29</sup> i.e. selectively non-selective drugs, underestimates the enormous challenge that this creates for medicinal chemistry.

The respondents gave a wide range of views on the future. There is a degree of optimism that new treatments will be coming forward, but not imminently. Some felt that the lack of a national strategy on CNS disorders to bring together pharmaceutical companies, academia and government was a hindrance to the successful development of new drugs for mental health in general. However, the creation of UK Clinical Research Collaboration (UKCRC) may provide a framework for such a development in the future. It is interesting that, at a European level, through the European Federation of Pharmaceutical Industries and Associations (EFPIA) and organisations such as the European Brain Council, the industry is promoting brain disease as an area for co-ordination of effort and investment. Many felt that new technologies would be important for future success. Pharmacogenomics and pharmacogenetics were frequently cited, although there was less agreement on when these techniques would really feed into the development of new treatments, with projections ranging from ten to twenty years ('a long march' as one described it). Certainly these techniques will be needed if we are to move from symptomatic treatment to early identification and prevention of disease. The genetic basis of depression may be understood within ten years, leading to greater patient segregation on the basis of prognosis and treatment modalities, as well as providing potential new targets and biomarkers to aid the drug discovery process. Some companies were optimistic that new understanding of neurotransmitter systems in cognition would bear fruit in providing cognition enhancers for a broader range of conditions, but probably in ten years rather than five. Others considered more radical approaches to therapy, such as implants and electrical stimulation of key brain areas, manipulation of gene expression through targeted activation of systemically delivered drugs, stem cell therapy (more than 20 years) and the use of small molecules to activate brain repair mechanisms.

Most respondents were highly optimistic that new antidepressants would be available in ten years and perhaps earlier. As before, this confidence reflects the fact that many major companies have active research programmes in this area that should deliver in this timeframe.

There was somewhat less confidence about new anti-anxiety drugs in the five-year horizon, despite the overlap between anxiety and depression and the new emphasis on stress disorders. But there was a degree of accord that in ten years new treatments should be available.



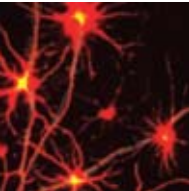
Cognition enhancement, whether for schizophrenia or for neurodegenerative disease, is clearly perceived as more challenging, for the reasons given above. There are many druggable targets implicated in processes of learning and memory, but the demonstration of robust clinical efficacy is neither fast, easy nor cheap. Mention was made of the importance of rehabilitation plus pharmacological intervention in effective therapy for neurological conditions. This applies equally for traumatic injury (e.g. stroke) and for degenerative diseases such as Alzheimer's. Concern was expressed that treatments intended to arrest cognitive decline, such as the promising anti-amyloid strategies being used in Alzheimer's Disease, could lead to the problem of long-term stabilisation of the impairment with no prospect of improvement. Obviously early and accurate diagnosis would be a key advantage.

The notion of preventative anti-psychotic drugs caused concern about how these would be developed and ethically tested in people. It would be necessary to be able to diagnose prodromal schizophrenia with great accuracy to justify the administration of drugs to those who are ostensibly well. The genetic basis of schizophrenia could be unravelled in 3–8 years and might provide the required diagnostic tools. There was a feeling that blocking the transition of the prodromal state to full-blown disease was challenging but not outside the bounds of possibility. Several respondents commented that advances in schizophrenia treatment are going to be difficult and that the more immediate future (5–10 years) lay in adjunct therapy in combination with atypical antipsychotics to broaden efficacy and reduce side-effects.

Many respondents listed other areas of mental health not covered by the main questions. Foremost among these was sleep disorder and the likelihood of new drugs within five years to treat lack of sleep, as well as addressing the need for increased wakefulness. Insomnia has been regarded as secondary to other conditions such as depression, but this picture is changing as it becomes increasingly recognised that insomnia is at the core of many CNS disorders and that treatment of insomnia will have a major impact on mental health. Successful treatments for stress disorders are likely in the 5–10 year timeframe as stress pathways are increasingly targeted for novel therapies. New treatments for ADHD, Parkinson's Disease (symptomatic), mood stabilisation and even, surprisingly, autism, were all mentioned by one or more respondents as likely within 5–10 years.

## **2.5 What is the likelihood of the development of new descriptions or definitions of mood disorders?**

There was a remarkable consistency in the responses to this question. New descriptions and definitions are expected with high probability in 5–10 years. One respondent felt that the development of new diagnostic criteria was



critical but not being given adequate priority for funding. The failure to improve outdated rating scales based on behavioural descriptors will impede our ability to incorporate genomic information arising in the next 5–10 years, which might then take as long as 20 years to become useful. For example, entirely different symptom clusters might add up to the same Hamilton Depression Rating Scale score, but it is unlikely that the underlying genetic factors are identical. More likely is that new descriptions and definitions will be based on treatment responsiveness and will thereby redefine the disease itself. For example, drugs reducing stress responses will probably be effective in a subset of so-called depressed patients whose exaggerated stress is responsible for their depression. These patients could therefore be re-diagnosed as suffering from a stress disorder rather than major depression.

Respondents were also in agreement that the development of new mood-altering drugs based on new definitions would eventually occur but would lag behind, with 15 years as the most likely time frame. Subclassification of symptoms associated with a core disease (e.g. cognitive impairment associated with schizophrenia) could lead to a clearer framework for polypharmacological approaches. Several warnings, though, were raised, such as the risk of blurring the boundary between therapeutics and 'cosmetics' a common concern with mood-altering drugs. Effective new medicines will inevitably be abused, in the sense that people will take them if they provide a pleasurable sensation, leading to psychological, if not physical, dependence. In an ideal world, such drugs would be used to help individuals susceptible to mood disorder and they would be provided with a proper mix of pharmacological and psychological support.

## **2.6 What is the likelihood of the development of specific drugs that are targeted to paediatric or geriatric care?**

Paediatric medicine is a difficult area for the industry and there was little consistency in the answers received. Some saw new drugs arising within five years, while others thought that 20 years was the minimum time needed to address all the questions. The safety issue is clearly uppermost in people's minds and is in marked contrast with the development of drugs for geriatric care where very long-term use and developmental toxicology do not require attention. One respondent commented that recent publicity over the use of antidepressants in children would overshadow the development of drugs for paediatric mental health for some time to come. ADHD has been more or less successfully tackled so the obstacles are not insurmountable, and new ideas about autism could bear fruit within ten years. The view was expressed that a focus on severe genetic or developmental illnesses would be ethically more acceptable than a focus on conditions for which behavioural therapy offers an alternative. However, developmental disorders such as autism have

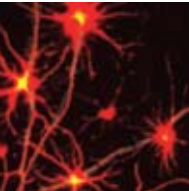
a poor prognosis and, even if treatments were available, toxicity issues would impede development, however efficacious the drug. As in many topics of this survey, the use of pharmacogenomic and pharmacogenetic tools to identify individuals at risk could change the balance in favour of new paediatric drugs.

There is more optimism in geriatric medicine. Current market opportunities are perceived as greater in today's climate, the hurdles are less severe (e.g. toxicological) and both of these are reflected in the emphasis that the industry is placing in mental diseases of old age, primarily Alzheimer's, Parkinson's, depression and sleep disorder. The latter should definitely be regarded as a primary medical problem in the elderly that remains largely unmet and contributes greatly to the tribulations of old age. In the care setting, one respondent expressed a wish for drugs to improve the quality of life of the elderly rather than just to sedate and manage them, a process that causes impaired rather than the improved cognitive performance that is needed.

One respondent pointed out that, despite the understanding that drug metabolism, efficacy and side-effects of drugs are age-dependent, clinical trials tend to be run in the 60–75 year age group, which is not geriatric by present-day standards.

## **2.7 Cultural, ethical, legal, societal, business or regulatory changes required to allow development of new drugs for medical purposes**

Every respondent thought that the industry would have a major role in providing information on the way to use drugs in the near future, the majority predicting within five years. Patients have progressed rapidly in recent years from being mere consumers of healthcare decisions made by the medical profession, through a stage of being better informed, to the present state in which they are involved in making decisions about their own care (the 'expert' patient). This change is desirable and inevitable, but does not necessarily make life easier for the physician or the patient. The access of patients via the Internet to various levels of information, from the traditional, academia-driven and peer-reviewed to the anecdotal, ill-informed and wildly illogical means that the industry should be in the forefront of initiatives to disclose data in order to protect themselves and their products. However, the industry has not moved fast enough in the eyes of the external world and the recent scramble to publish clinical trial data has been motivated more by external legal proceedings than by a genuine desire for openness. As one respondent put it, accusations of lack of transparency over the effects of Vioxx (rofecoxib), Seroxat (paroxetine) and Prozac (fluoxetine) has increased the public's suspicion of the industry, forcing greater openness on the one hand and a demand for more drug monitoring on the other. Nevertheless more



openness is a good move and nearly all respondents were of the opinion that complete reporting of all clinical trial data will be the norm within five years, whether this is voluntary or legislated. A separate issue is how the information that individual companies hold on their products can be conveyed to the patient. National policies on direct-to-consumer advertising differ widely, but patient groups do not want gatekeepers controlling the information they are allowed to receive.

Changes in the way drug discovery is done and delivered to the patient will also have an impact on the transparency issue. The expected development of personalised medicine will lead to the industry offering both diagnostic tools and treatments, bringing them much closer to the patient and requiring more data disclosure and a greater involvement of the patient in decision making.

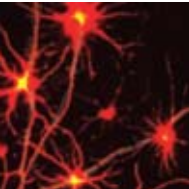
The industry would like its increased openness to be accompanied by improved understanding on the part of external stakeholders. Public education will be needed and the industry will have to make efforts to provide information in a way that the public can understand. Regulatory agencies have a major role to play in interpreting data in a rigorous and dispassionate manner that strikes a fair balance between the pros and cons of a treatment option. Knee-jerk responses to setbacks may be an inevitable response to the threat of litigation but do little to benefit the patient. Several voices from outside Merck commented that the Merck's defensive withdrawal of Vioxx from the market made no medical and scientific sense and severely limits treatment options for patients in need. Significantly, since these comments were received, the US Food and Drug Administration has given its cautious blessing for Merck to allow Vioxx back onto the market, but only under severely restrictive conditions.<sup>8</sup>

The need for public debate and understanding is most necessary in areas of greatest sensitivity, for example, where treatment could be imposed for perceived individual or societal gain. With regard to vaccines for the treatment of addiction, the role of the pharmaceutical industry in providing information on the way to use such drugs in the future will be very important but possibly quite restricted. The clinical studies that will be needed to understand the limits to the use of these vaccines as a therapy and as a preventative will be strongly influenced by the regulatory authorities. While the latter are very keen to support the development of new, effective therapies to help current addicts, they may have a strict view about running studies in adolescents to establish the impact these vaccines have on preventing the initiation of drug taking. This aspect of vaccine use in addiction has not yet been discussed in any detail, but will likely involve a number of different social, ethical, government, and regulatory and pharmaceutical groups.

Most respondents believed that regulatory and societal changes will therefore serve to both help and hinder new developments in mental health. On the positive side, greater transparency and a better-informed public debate on risk and benefit could lead to an appreciation that drugs can never be absolutely safe. This appreciation could help counter the present negative image of the industry, restoring confidence in and within the sector and removing the dead hand of risk-averseness from initiatives to develop innovative treatments. Nevertheless, many respondents felt that the inevitable price of recent events would be more post-launch monitoring for side-effects, and more regulation to protect patients, even at the cost of creating barriers to drug discovery. An interesting alternative view was put forward by one respondent who believed that a combination of patient demand and funding problems would eventually reverse the trend towards greater safety as soon as the baby boomers really reached old age. The choice could be either to lower the regulatory hurdle for approval of new treatments in order to lower the costs of care, or to legalise euthanasia.

## **2.8 What psychoactive substances could be developed specifically for non-medical purposes?**

The attitude conveyed by the responses from the industry ranged from 'impossible' to 'why not?' The essential issue which all recognised was that scientifically there is no reason why not, but the question is whether society is prepared to accept this development. As described in Section 1.3, this question was not about the off-label use of drugs developed for medical purposes (Section 1.2), although several respondents chose to focus on the ethical, legal and social acceptability of mental performance-enhancing drugs rather than the route by which they were developed. Consequently the timelines vary enormously. Several respondents felt that cognition and attention enhancers might be available in ten years, but this implies that the industry is currently working on drugs for strictly non-medical purposes, which is certainly not the case. However, there are shades of grey between the all-white of purely medical and the black of totally non-medical. Drugs might be developed for particular medical conditions that drive clinical trials and allow the regulators to approve the drugs, when in fact no one is fooled into thinking that they will be restricted to that use. The obvious example that several respondents quoted is that of modafinil (Provigil), approved for the rare condition of narcolepsy, but widely used and prescribed for dealing with various conditions of sleep deprivation, few of which would be considered medical. The regulatory path to create a purely non-medical drug for sleep-deprived, overworked western man and woman is now clear and will no doubt be taken again in the future.



In their comments, many respondents tackled the general ethical issues around this topic. Taking the question in its intended literal sense, most thought that the answer was that it would never be possible to develop drugs in the foreseeable future purely for non-medical uses, even if those uses were acceptable to society. Major social change would be required to permit this to happen. As one correspondent put it, we are already in the era of non-medical drugs, it is just that we prefer not to admit it yet. What percentage of Viagra (sildenafil) sales is for genuine male erectile dysfunction? Is the enormous effort devoted by the industry to obesity just intended for those whose weight poses them a serious medical problem? We are already beginning to treat deviation from the norm rather than a specific medical condition. Perhaps normalising blood pressure in patients with hypertension was an early example of this. The societal change needed is greater honesty about what we really want, but this could take many years. The industry is reluctant to push the issue because of the impossibly high standards of safety that would be demanded of a drug developed exclusively for non-medical use. However, greater societal acceptance (or honesty) in this regard would deflect current criticism of the industry, that it creates diseases in order to sell its products (such as ADHD), as the link between what the industry produces and medical need would be severed and replaced by what society wants. The debate about whether industry is trying to move the defining line of normality would become irrelevant.

However, in the current climate, the industry is very sensitive to these issues and, not surprisingly, cautious. Defining the border of normal is difficult, as one respondent said. Another described the issue in terms of public attitudes to increasing performance, providing pleasure and decreasing the stress and strains of daily living. If athletes provide themselves with the best of nutrition to optimise their physical performance, what is to stop the public demanding chemical nourishment for their brain processes? If it really works and is safe, acceptance would be inevitable, although demonstrating efficacy and safety is not trivial.

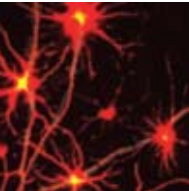
The safety question may be the greatest impediment to the industry, which is why many respondents thought that the only route to non-medical use was via the demonstration of safety and efficacy in a medical condition. Screening for potential abuse in both animal and human studies is a regulatory requirement and the industry would consider this as part of the entire risk–benefit profile before deciding to continue development of a medicine. A positive screen or abuse test is seen as a major issue, with implications for storage, distribution and ease of writing prescriptions. So it would only be pursued as a medicine if the medical benefit was considerable. Furthermore, the risk to those taking part in clinical trials is counterbalanced by the potential therapeutic benefits. Regardless of society's acceptance or desires, the industry seems likely to adopt this lower-risk approach and, even then,

there would need to be increased public awareness that drugs for non-medical uses still carry risk. It would be easy for the general public to assume that such products were inherently safer than drugs for medical conditions, in the way that many people already take drugs such as ecstasy on a regular basis with little concern for the consequences. As one respondent put it, 'just because you can buy it, doesn't mean it is safe.' A happy pill will always be open to abuse and there will always be the suspicion that industry is putting people at risk for profit, and that Government permits this in order to avoid dealing with the root causes of drug-seeking behaviour.

The types of non-medical use that the respondents identified included mood enhancers, anxiolytics, sleep promoters, wakefulness promoters, impulsivity controllers, reaction time modulators and vigilance enhancers. All of these could have *bona fide* medical uses as well. The most likely in the 10–20 year timeframe were cognition enhancers, drugs to improve attention (a better caffeine) and drugs to deal with sleep disturbance. There was no agreement on whether it was likely that substances such as nicotine could be delivered in drinks. The response was probably "yes, but why bother?"

## **2.9 Are there any other key broad issues not covered elsewhere?**

There were few responses in this section and of these, several had already been considered by others in their responses to previous questions. Here two themes are picked out which resonated with many of the comments received. The first is that the successful development of new drugs for mental health would be greatly aided by better national co-ordination of research efforts as already occurs in the US, and that there should be better collaboration between Government, the industry and academia to focus resources on critical areas of need. The now defunct UK National Neuroscience Research Institute was an attempt to do this, and it is to be hoped that the UKCRC will help to bring together a national strategy for mental health. Failing this, the European initiatives mentioned earlier may provide a suitable framework. The second is that the treatment of mental illness will change. Better diagnosis and risk-factor assessment, the use of imaging and other technologies will aid appropriate pharmacological intervention. But proper treatment will need to integrate this with behavioural and psychological approaches. As has already been said, there are no magic bullets for mental illness.

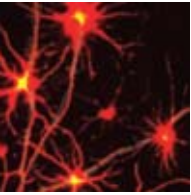


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# Appendix 1: Acknowledgements

The author would like to thank all those companies who participated in this survey and gave so freely of their time and opinions.

They were:

Amgen  
GSK  
Lilly  
Merck  
Neurocrine  
Pharmidex  
Pfizer  
Roche  
Xenova

# Appendix 2: Survey material

Appendix 2 contains a copy of the letter sent to companies inviting them to participate in the study and also a copy of the questionnaire used to collect data.

## Copy of the letter

The aim of the Foresight on Brain Science, Addiction and Drugs project is to look to the future situation in 2025 and beyond, to consider various ways in which psychoactive substances might be produced, used and regulated. Psychoactive substances are those that are for mental health, pleasure, to enhance cognition or to modify mood.

The key question that the project is addressing is:

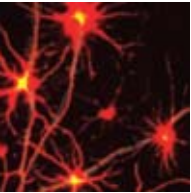
*How can we manage the use of psychoactive substances in the future to best advantage for the individual, the community and society?*

Foresight has commissioned 15 state-of-science reviews to provide a scientific basis to explore the key question. The project is looking at a 20 year timeframe, so we are thinking about 2025.

This review was commissioned to ensure there was input to the project from an industry perspective. The attached questionnaire is to help you formulate your responses and to enable the writing of a consensus industry view of 2025. The survey is based around three main questions, with a fourth section to cover anything that you consider important which is not covered elsewhere in the survey. These three questions are:

- What will be the psychoactive substances of the future (for medical purposes)?
- What regulatory and societal changes would be required to allow these drugs (for medical purposes) to be developed and marketed?
- What psychoactive substances could be developed specifically for non-medical purposes?

Obviously any information you can provide should be non-confidential and will be non-attributable. The companies that participate in this survey will be listed and thanked for their input but comments from individual companies will not be



identified. I hope that this will encourage the free flow of creative and imaginative juices and therefore please do not feel constrained by the size of the comments boxes. Put down everything that occurs to you. It is likely that the report that is written will eventually be made available publicly though publication in a report in hard copy or downloadable from a website.

The timescale of this exercise is unfortunately very short and, therefore, if you are unable to participate because of lack of time, please delegate the job to those who have, or preferably get a small group to brainstorm the questions. I would appreciate your response by 4 February 2005 at the latest.

Thank you for your time and assistance.

C. Ian Ragan

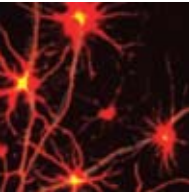
# Copy of questionnaire

## Section 1 of the questionnaire

We would like you to speculate about what types of psychoactive substances there might be in the future. We would like you to consider the role that advances in pharmacogenetics and pharmacogenomics and other technologies will play in realising these developments and the extent that the field could move from symptomatic treatment to cure, prevention or disease modification.

Where possible, please indicate the probability of such developments in the times shown. A separate box is available for you to comment on these or other developments of these types and to expand on your responses.

<b>1. What new preventions/treatments for addiction and problem use may be developed in the following areas?</b>	<b>5 years</b>	<b>10 years</b>	<b>15 years</b>	<b>20 years</b>	<b>Never</b>
Vaccines (for prevention and treatment)					
Drugs to enhance executive function					
Drugs to unlearn addiction					
Anti-stress drugs (as stress has been associated with relapse)					
Combinations with psychological approaches					
Other preventions/treatments not listed that you think the project should consider and when they might be developed					
Comments (e.g. scientific constraints, impact of technology, genomics etc)					

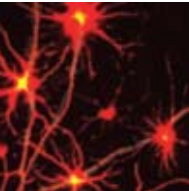


<b>2. What is the likelihood of new treatments for the management of pain?</b>	<b>5 years</b>	<b>10 years</b>	<b>15 years</b>	<b>20 years</b>	<b>Never</b>
What is the likelihood of there being effective drugs that do not carry the risk of abuse?					
Comments (e.g. scientific constraints, impact of technology, genomics, other management of pain issues not listed that you think the project should consider)					

<b>3. What is the likelihood for the development of new drugs for mental health in the following areas?</b>	<b>5 years</b>	<b>10 years</b>	<b>15 years</b>	<b>20 years</b>	<b>Never</b>
New antidepressant drugs					
New anti-anxiety drugs					
Cognition enhancement for those with Schizophrenia					
Cognition enhancement for those with neurodegenerative conditions e.g. Parkinson's Disease, stroke, brain injury					
Preventative anti-psychosis drugs					
Other drugs for mental health not listed that you think the project should consider and when they might be developed					
Comments (e.g. scientific constraints, impact of technology, genomics, opportunities for disease modification etc)					

<b>4. What is the likelihood of the development of new descriptions/definitions of mood disorders?</b>	<b>5 years</b>	<b>10 years</b>	<b>15 years</b>	<b>20 years</b>	<b>Never</b>
If so, is it likely that this will lead to the development of new treatments?					
Other issues to do with the development of mood-altering drugs not listed that you think the project should consider and when these might arise					
Comments (e.g. impact of genetics, pharmacogenetics, pharmacogenomics etc., possible new or redefined mood disorders)					

	<b>5 years</b>	<b>10 years</b>	<b>15 years</b>	<b>20 years</b>	<b>Never</b>
<b>5a. What is the likelihood of the development of specific drugs that are targeted for paediatric care?</b>					
<b>5b. What is the likelihood of the development of specific drugs that are targeted for geriatric care?</b>					
Other issues to do with the development of mood-altering drugs not listed that you think the project should consider and when these might arise					
Comments (e.g. impact of genetics, pharmacogenetics, pharmacogenomics etc., possible new or redefined mood disorders)					



## Section 2 of the questionnaire

For this section we would like you to consider what cultural/ethical/legal/societal/business/regulatory changes may be required to allow drugs (for medical purposes) to be developed and marketed. Where possible, please give some indication of the importance or likelihood of such developments in the times shown (e.g. little, a lot, etc). A separate box is available for you to comment on these or other developments of these types and to expand on your responses.

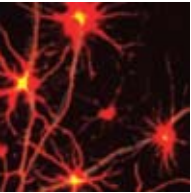
	5 years	10 years	15 years	20 years	Never
<b>6. How important a role will the pharmaceutical industry have in providing information on the way to use drugs in the future?</b>					
<b>7. How open will be the disclosure of research results?</b>					
<b>8. Will changes in context, whether regulatory or social, occur which will help or hinder advances in these developments or their deployment?</b>					
<b>9. Will there need to be greater safeguards in drug use, for example through drug monitoring?</b>					
Other – any issues not covered by questions 6–9 that you think the project should consider and when these might arise					
Comments (e.g. communication of information, disclosure of research results, nature of societal changes)					



## Section 3 of the questionnaire

In Section 3 we would like you to speculate on what psychoactive substances could be developed specifically for non-medical purposes. Where possible, please indicate the likelihood of such developments in the times shown. A separate box is available for you to comment on these or other developments of these types and to expand on your responses.

	5 years	10 years	15 years	20 years	Never
<b>10. What is the likelihood of the development of drugs specifically for non-medical use?</b>					
<b>11. What would these drugs be? Please make suggestions with probabilities and times</b>					
<b>12. What changes would be needed in society, in the development and regulatory processes and in the market to allow this? Please list, with likelihood.</b>					
<b>13. What is the likelihood of delivering products such as nicotine in drinks?</b>					
<b>14. What is the likelihood of delivering cognition enhancers that could be used for non-medical purposes?</b>					
Other – any issues not covered by questions 10–14 that you think the project should consider					
Comments					



## **Section 4 of the questionnaire**

Are there any other key broad issues that are not covered elsewhere in this survey that are being driven by advances in science capability that you think the project should consider? If so, please would you comment?

# List of publications: Drugs Futures 2025?

All publications are available in hard copy and/or can be downloaded from the Foresight website except those marked \*\*\* which are available only from the website ([www.foresight.gov.uk](http://www.foresight.gov.uk)).

1. Executive summary and project overview
2. State-of-science reviews \*\*\*
  - I. Cognition Enhancers
  - II. Drug Testing
  - III. Economics of Addiction and Drugs
  - IV. Ethical Aspects of Developments in Neuroscience and Addiction
  - V. Experimental Psychology and Research into Brain Science and Drugs
  - VI. Problem Gambling and other Behavioural Addictions
  - VII. Genomics
  - VIII. History and the Future of Psychoactive Substances
  - IX. Life Histories and Narratives of Addiction
  - X. Neuroimaging
  - XI. Neuroscience of Drugs and Addiction
  - XII. Sociology and Substance Use
  - XIII. Social Policy and Psychoactive Substances
  - XIV. Psychological Treatment of Substance Abuse and Dependence
  - XV. Pharmacology and Treatments
3. State-of-science reviews (2 page summaries)
4. Ethical issues and addiction overview \*\*\*
5. Horizon scan
6. The scenarios
7. Public perspective
8. Perspective of the pharmaceutical industry
9. Modelling drug use











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