Pharmacology Matters

BRITISH PHARMACOLOGICAL SOCIETY
Today's science, tomorrow's medicines

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The Newsletter of the British Pharmacological Society
Volume 3 Issue 2, December 2010

Drugs of Abuse

Alcohol | Cannabis | Mephedrone | Ritalin | Drug Abuse – Educating Today's Teenagers

BPS | BRITISH PHARMACOLOGICAL SOCIETY

Chancellor's Building
Royal Infirmary of Edinburgh
Scotland
28 January 2011

Hypertension

CPD approval applied for

Organizers:

Professor David Webb
& Dr James Dear
The University of Edinburgh

Programme:

08:55 Introduction

09:00 Epidemiology and the clinical burden of hypertension
-Professor Tom MacDonald

09:30 Does it matter how we measure BP?
-Professor Paul Padfield

10:00 Does it matter where we measure BP?
-Dr Ian Wilkinson

11:00 Cardiovascular risk assessment and workshop
-Dr Rupert Payne

13:00 Drugs used to treat hypertension
-Professor Simon Maxwell

13:30 Clinical trials in hypertension and workshop
-Professor Gordon McInnes

15:00 Guidelines for management of hypertension
-TBC

16:00 Future strategies for hypertension management:
Renin profiling
-Professor Morris Brown

Genetic profiling
-Professor Aroon Hingorani

£75.00 (academia): £150.00 (industry)

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Editorial

We welcome contributions from our readers, all suggestions should be e-mailed to the Managing Editor: hom@bps.ac.uk

Front cover Image: istockphoto.com

Recreational drug taking is a subject that sparks intense and often polarized debate. This issue explores the subject from a pharmacological perspective and examines the physical effects of: mephedrone, alcohol, cannabis, and cognitive enhancers.

Over the last 12 months the dangers of taking 'legal highs', such as mephedrone, made numerous headline appearances, catalyzed by links to the tragic deaths of several people. David Wood and Paul Dargan's article on pg 11 explores the chemistry of mephedrone, how it is (ab)used, and explains the real and perceived risks to users.

Cannabis and cognitive enhancers, when taken recreationally, produce very different physical outcomes but have proven clinically effective in the management of pain and central nervous diseases. Nikolas Dietis and Thomas Longden contemplate the increasing availability and recreational use of cognitive enhancers on pg 9. Roger Pertwee discusses the pharmacology, medicalisation and recreational use of cannabis on pg 14.

Alcohol is often considered separately from more obvious drugs of abuse such as cannabis and mephedrone, but alcohol dependence costs the NHS around £3billion per year, and is 'used' in varying degrees by 90% of the adult population. Professor David Nutt's 9-category matrix of harm published in his controversial lecture *Estimating Drug Harms: a risky business*, ranked alcohol as more harmful to society than cannabis and LSD. Hilary Little's article, pg 16, considers the impact of this more socially acceptable drug, as well as current developments in pharmacological treatment for alcohol dependence.

This issue also contains a comprehensive guide to the proposed changes to the BPS constitution. I would invite you to read this information carefully and direct any questions to Kevin Kearns (kjk@bps.ac.uk) before the BPS Annual General Meeting, which takes place on 16 December.

Enjoy

Hazel O'Mullan

Managing Editor

Contents:

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View from Angel Gate

Kate Baillie
Chief Executive, BPS

The view from Angel Gate today is distinctly Autumnal! It seems aeons ago that we were in Copenhagen in positively tropical conditions for the World Pharma Congress in July! In spite of the difficult economic situation, the event was a resounding success and attracted over 3000 delegates from 80 countries.

Dr Jeffrey Aronson, BPS President Emeritus, opened the Congress with his plenary lecture, *Found in translation, human pharmacology & applied pharmacology come of age*, which provided an ideal opportunity for a spot of 'guerilla marketing' outside the lecture theatre for BPS journals, meetings and membership information!

The three BPS-organized and sponsored focused meetings were extremely well attended, we even had delegates queueing to attend some of our sessions. BPS was also delighted to provide support to the EPHAR lecture, *Successes and Challenges in Drug Development - a Regulatory Perspective*, presented by Thomas Lönngren from the EMEA.

Another successful BPS- sponsored initiative during the Congress was the Young Pharmacologist's Social Event. BPS Young Pharmacologists organized a networking event with colleagues from the Danish Pharmacological Society, which attracted attendees from as far away as Bangladesh, Australia, Serbia and the US. One delegate was so taken with the event, that she wore her BPS YP's committee "I love Pharmacology" T-shirt to present her paper the following day!

As well as providing support to the scientific programme and networking opportunities, BPS staff and Officers were on hand throughout the meeting, at the new BPS stand, providing information about BPS and encouraging delegates to join. One suggestion we received was to provide BPS promotional materials and BPS banner stands for use in members' departments. Please let me know if you would be interested in taking up this offer, and we can arrange for materials to be sent to you.

Over the past few months, the group set up by Professor Ray Hill, BPS President, to look at the needs of members in industry and bio-tech has made great progress under the Chairmanship of Martin Todd. A whole series of activities has been planned, including development of a consultancy network; preparations for the first industry group James Black conference in September 2011 - *Drug Discovery for the New Millennium; Riding the Biological wave*; support in the form of free membership and networking opportunities for those who have been made redundant as a result of restructuring within companies, and plans for a BPS Careers workshop at the One Nucleus 10th Anniversary Genesis meeting on 9 December in London. This forum facilitates meetings between emerging life science companies and potential investors and technology partners, and provides a forum for debate, led by high level keynote speakers. We are also hoping to investigate establishment of a mentoring scheme and exploring ways in which BPS can support the Open Innovation agenda.

In memory of Sir James Black, and to celebrate the achievements of our members who work at the cutting edge of drug development making a valuable contribution to public health and to 'UKPLC', we have set up the Sir James Black Award for Contributions to Drug Discovery. This award of £1,000 will be given where, in the opinion of the Society, there has been a demonstrable contribution to drug discovery in application or use. Nominations, of individuals or teams of up to five people, can be made by any member of the BPS, and can be submitted at any time during the year. Further details are available on the BPS website.

BPS outreach activities have continued in this period with a popular session at the British Science Festival presented by Roger Pertwee *Cannabinoid research: is the grass greener?* Roger's talk attracted considerable attention in the national press.

Pharmacology also celebrated success at the recent SET Awards, where Rebecca Barlow, Leeds University, was awarded both the AZ prize for Best Pharmacology Student and the top prize as SET Student of the Year. Dr Alan Bateson, also from Leeds was awarded the Lecturer of the Year prize.

Development of the new BPS website is now available at www.bps.ac.uk offering additional functionality, including the facility for members to form virtual communities. We have also started a virtual archive containing video interviews of key pharmacologists, commencing with Professor Gus Born and Professor Alan Cuthbert.

Another new initiative taking place at the BPS Winter Meeting, London 2010 will be the inaugural BPS President's Public Lecture, which will be given by Professor Les Iversen, entitled *Bringing Cannabis Back into the Medicine Cabinet*. We hope this will provoke a lively debate and provide BPS with further opportunities to engage in outreach activities to the general public.

Kate Baillie MA MBA, Chief Executive BPS

Renewing our constitution:
your guide to the proposed changes

Ray Hill, BPS President

In the last few months, the BPS Office has been reviewing our constitution, to ensure it fits the Society's future objectives, and meets a host of recent legislative changes. Our colleagues at Angel Gate have taken professional advice and been guided by several senior members in what has been a lengthy and comprehensive review process.

The current document was found wanting in several respects, and the Trustees therefore wish to propose adopting a revised constitution. If the Trustees' proposed revisions are adopted the Society will remain a membership institution with its governing body (Council) elected by the members.

The final stage of the process will be to put the proposals to our members for consideration, and this will be done at our Annual General Meeting on 16th December 2010. Before that, members will be able to cast their vote on these important amendments by post or, for the first time, using an online system supplied by the Electoral Reform Services – more on this in Q6 in the Questions & Answers session below.

In the interim, may I recommend that you have a look at the revised Articles of Association (which can be found in the Members' Area of the Society's website under "Member Information")? We have also published a Questions & Answers bulletin explaining why the revisions have been necessary and either Kevin Kearns at the BPS Office or I will be very happy to answer any further queries by email at kjk@bps.ac.uk or president@bps.ac.uk respectively.

Yours sincerely

Prof Ray Hill FBPharmacolS; FMedSci

BPS President

Questions & Answers Bulletin

Q1. What are the Society's "constitutional documents"?

A. The Society is both a registered charity and company limited by guarantee. This means that instead of just having a set of rules (or trust deed) defining its charitable purpose and powers, it must also have a Memorandum and Articles of Association. The Memorandum basically sets out why the company has been formed and its powers and the Articles of Association sets out the rules by which the company must be managed. When the Society became a company limited by guarantee in 1993, it chose to merge its then rules with its Memorandum & Articles of Association. We refer to this merged document as the Society's constitution.

Q2. Why has it been necessary to propose revisions to the constitution?

A. There are essentially three reasons:

(i) At present the Society needs to convene a formal meeting of all its members before it can make changes to the rules which govern its day to day operations. Our current constitution delegates responsibility for the day to day operations of the Society to the Executive Committee. The Executive Committee is often unable to respond effectively and efficiently to enhance or improve the Society's ability to deliver services to members and stakeholders, because part or all of a change might involve a change to the wording of the constitution, which cannot be made without the approval of all members in general meeting.

(ii) Although many of the Society's main committees are mentioned in the current constitution, others are not. For example the Finance Committee, which advises both the Executive Committee and the Council on the Society's finances, investments and operational risks, is not mentioned at all. Whilst this might have been acceptable some years ago, the Society is now financially much larger and involved in a greater range of activities and our auditors recommend that the remit of the Finance Committee (recently renamed Finance & Risk Committee) should therefore be formally recorded.

(iii) The current rules were adopted in 1932 and the current Memorandum and Articles of Association were adopted in 1994. In addition to the numerous subsequent changes to the original rules there have also been 12 major changes to the Articles of Association resulting in a constitutional document which is very difficult to follow. More importantly, the constitution as currently drafted does not lend itself to effective, efficient governance. In addition, the period 2008-09 saw wholesale change to the way in which companies must be managed, brought about by the introduction of The Companies Act 2006. Most of these legislative changes are clearly advantageous for the Society and although we adopted some in 2008 (e.g. the ability to communicate electronically with our members on governance issues such as this) it is very clear that the document has now reached its useful capacity.

Q3. So how does the Society propose to address the issues mentioned in Q2? How will this affect the way the Society is run?

A. After consulting our legal advisers, we decided to adopt a process seen as best practice in many similar organisations. This involved separating the operational rules from the Memorandum and Articles of Association and adopting a set of modern, revised Articles of Association acceptable

to the Charity Commission (who regulate our charitable work) and Companies House, who regulate the way we operate as a company limited by guarantee.

The revised Articles set out how the Society is governed and its powers, and the Council's obligations to the Society and its members; and members continue to have limited liability (up to £1.00 each) for the debts and liabilities of the Society. Should the revised Articles be adopted, any future changes will continue to require the approval of all members in General Meeting. The constitutions and remits of the Executive Committee and the Finance & Risk Committee are now clearly defined in the proposed Articles.

The operational rules, dealing with how the Society's day to day business is managed have been moved to a new Rule book. Changes to the Rules will require approval by the Executive Committee and ratification by the Council, although certain Rules (for example those dealing with the membership structure, membership fees and the election of trustees and officers) will still require final approval by members in General Meeting. The constitutions and remits of all of the Society's sectional committees (e.g. Meetings, Clinical Section, and Education & Training) will be recorded in the Rules making it easier for the Executive Committee and Council to respond to new opportunities.

Q3. Does this mean that the Society is no longer a member organisation?

A. Absolutely not. We have gone to great pains to retain the existing structure and charitable objectives of the Society, transposing them faithfully to the new Articles. The members still elect the Council and Society Officers and any member can stand for election to any post. There can be no alteration to the existing corporate identity of the Society (a UK registered charity and company limited by guarantee) nor to the objectives of the Society without the approval of members. Revenues from our journals and other activities must still be used exclusively towards the Society's objectives (to promote pharmacology, including without limitation clinical pharmacology).

Q4. Are any additions proposed to the current Articles?

A. To ensure that we are ready and able to meet potential challenges in the future, we have taken the opportunity to seek the Charity Commission's agreement to include several new Articles in the revised document:

(i) The introduction of a new post of "Treasurer-elect". The Treasurer-elect, although elected in the exact same manner as the Honorary Treasurer, will be a member of the Finance Committee but will not be a trustee or officer of the Society, until he/she takes over as Honorary Treasurer, usually after serving for one year as Treasurer-elect. We propose the introduction of this position to improve succession planning for this senior role and also to provide greater continuity for the financial management of the Society.

(ii) The introduction of lay members of the Council, who might not necessarily be members. Occasionally, the Society might benefit from expertise or services not readily available within the membership and this option provides the opportunity to recruit such expertise for specific purposes. Where members of Council provide a specific piece of expertise, consultancy or services (but not ordinary trustee's duties) the Executive Committee, with the support of the Finance & Risk Committee, can agree appropriate remuneration.

(iii) The option to establish a trading subsidiary. Although there are no current plans to do so, this can be a useful option if we are presented with the opportunity to diversify our income. Raising income through trading can have significant tax advantages if done through a trading subsidiary and whilst the trading liabilities rest with the subsidiary, the Society's charitable assets remain protected within the Society.

Q5. What are the next steps?

A. We imagine that some members may well have queries regarding the proposed changes and both Kevin Kearns (kjk@bps.ac.uk) and the Society's President, Ray Hill (president@bps.ac.uk) will be very happy to respond. In the interim, a copy of the proposed revised Articles of Association can be found in the "Member Information area of the Society's website and a copy can also be obtained by contacting Kevin at the BPS Office (020 7239 0173). Copies of the existing [Memorandum, Articles of Association and Rules] can also be obtained from Kevin. The revised Rules will be available in early December 2010.

When the documentation for the Annual General Meeting is sent out (approximately 17 November 2010) the Agenda will make reference to a resolution to: "Adopt, effective 1 January 2011, the revised Articles of Association in substitution for the current Articles of Association". All members eligible to vote will be asked to cast a vote in favour of the resolution. The Council sincerely hopes that you will support its proposals, which have been crafted with the guidance of several of the Society's senior members.

Q6. Tell me more about the procedure for casting my vote

As some 90% of our members have now chosen (following the 2008 AGM), to receive information regarding corporate governance matters electronically, we have decided to further enhance this aspect of environmental responsibility by inviting members to cast their votes electronically at the 2010 AGM. In fact there will be three methods for members to cast their votes at the AGM:

(i) for those of you who have chosen to receive corporate governance information electronically, you will be able to vote securely and confidentially online via Electoral Reform Services ("ERS"), OR you can cast a postal vote by printing and returning the electronic ballot paper to ERS, OR you can vote in person at the AGM;

(ii) for those who have chosen to receive corporate governance information by post, you will receive a ballot paper which you will need to complete and return to ERS, OR you can vote electronically OR in person at the AGM;

(iii) for those able to attend the AGM , which will be held during the 2010 Winter Meeting on 16 December, you can vote in person but please note that you can only do this if you have not already voted by electronic or postal ballot.

The services provided by ERS are confidential and electronic voting is secured by a two-part security code; whilst a signature will be required for postal votes. Please remember that we can only communicate with you if your contact details are up to date. You can review these by logging onto the members' area of BPS website (www.bps.ac.uk) and making any necessary changes to you Profile details. If you need any help in this respect, please don't hesitate to contact Paul Tizard at the BPS Office (pt@bps.ac.uk) or on 020 7239 0171.

Why understanding the pharmacology of drugs of abuse may help educate teenagers about the risks associated with drug abuse and drug addiction

Emma S J Robinson and Neil V Marrion

Emma S J Robinson and Neil V Marrion, University of Bristol

Dr Emma Robinson is a Senior Lecturer in Pharmacology in the School of Physiology and Pharmacology, University of Bristol. She completed her degree in Pharmacology at the University of Bristol and PhD in the Psychopharmacology Unit, University of Bristol and Knoll Pharmaceuticals, Nottingham. In 2005, she was awarded and RCUK Academic Fellowship in the priority area of integrative pharmacology with support from the British Pharmacological Society Integrative Pharmacology Fund. Specializing in studying the brain mechanisms that control normal and abnormal behaviour, her research investigates the cause and treatment of psychiatric disorders such as depression, anxiety, ADHD and addiction.

Neil Marrion is a Professor of Neuroscience in the School of Physiology & Pharmacology at the University of Bristol. He worked as a postdoc with Professor Paul Adams in SUNY Stony Brook for five years, after gaining his B.Sc. from UCL and his Ph.D. from the School of Pharmacy. He was a faculty member at the Vollum Institute, Portland, Oregon for five years, before returning to the UK to take up his position at Bristol. His laboratory uses electrophysiology, molecular biology and biochemistry to study the functional role of potassium channels in neurons and cardiac muscle.

Summary

Public engagement in science offers a range of opportunities for individuals involved in cutting edge research to discuss their work with members of the public. One of the main areas where interaction between scientists and the public is best achieved is through links with schools and events targeted at school audiences. Of the topics most popular with 14-18 year olds, drugs of abuse and sexually transmitted diseases are top of the list. This suggests that teenagers feel they need more information on these topics, are keen to hear from scientific experts and/or feel they are not given sufficient information though other routes. Pharmacologists are ideally placed to enhance public understanding of drugs of abuse and provide unbiased information and discussion about what drugs are, how they affect the body and their ability to cause serious harm. This offers potential educational benefits as it can explain why people react differently to drugs, the risks associated with both legal and illegal drugs of abuse, why drugs of abuse can lead to addiction, and the detrimental effects they may have on individuals. Describing work in animal models can provide powerful examples of how drugs themselves can alter behaviour. This article summarizes some of the material discussed with teenage audiences on the subject of 'drugs of abuse'

The pharmacology of drug abuse

The term 'drug' within the public domain is usually associated with an illicit substance whilst the term 'medicine' is used to describe substances with therapeutic benefits. Interestingly, substances such as alcohol and tobacco tend not to be considered 'drugs'. Pharmacologists consider that a key component to understanding the way a 'drug' affects biological systems is an explanation of drug-receptor interactions. This leads onto explanations of how the dose of the drug influences its effects and its likelihood of causing an adverse response. A relatively brief explanation of 'drug-receptor' theory can illustrate how drugs of abuse alter the function of cells in the body to mediate their pleasurable effects, but also how they potentially cause harm. What is clear is that most schoolchildren aged 14 plus are aware of the pleasurable effects of taking a drug of abuse and many will have either personal experience or will know friends who have taken them. However, few understand how a drug might affect their bodies or why they can be damaging in both the short and long term. This raises a potentially difficult issue. Existing sources of information given to schoolchildren (e.g. FRANK) list the form the drug is available in, how it is taken, the effects, the street price, the legal class, and possible risks. An educational problem arises because many schoolchildren have had experiences suggesting to them that drugs cause little or no harm, and

"... many schoolchildren have had experiences suggesting to them that drugs cause little or no harm."

in some cases they would argue that their experience contradicts the advice and literature they are given.

What is drug abuse and drug addiction?
Drug abuse is defined as the taking of a pharmacological substance for non-medicinal purposes. Of the total population who use drugs for recreational purposes, only a proportion will go on to develop drug addiction as defined by DSM-IV criteria. The potential to develop addiction to either a legal or illegal substance is probably the greatest overall risk, yet is perhaps the least well explained in terms of education. Estimates vary but up to 20% of people who start using drugs for recreational purposes are thought to develop drug addiction. It is true to say that some problems arise because the drug information sources have not been able to keep up with new drugs that are likely to be highly addictive (e.g. oxycodone). But educational messages often do not emphasize how and why drugs of abuse alter our behaviour, why the drug itself can influence our ability to make rational judgements and why drug addiction is the most serious, and difficult to control, outcome associated with repeated use of both legal and illegal psychoactive substances.

The taking of psychoactive substances is not limited to humans and a number of examples have been noted of animals actively seeking, and taking drugs for their psychoactive properties. A wide range of species seek out fermenting fruits and many people have seen the effects of cat nip on their household pet. Why animals seek these substances is likely because, as in humans they activate reward pathways in the brain. Whilst reward itself serves an important survival role by directing behaviour to obtaining resources of value whilst avoiding harm, these brain regions are activated by psychoactive drugs. In contrast to the behaviour seen in most animals, some humans develop addiction where the need to take drugs overrides all other behaviours. The reason why some develop addiction whilst others do not is complex and much is still unknown, but genetics and environmental factors such as stress are thought to play key roles. Animals maintained under laboratory conditions can be used to model the compulsive behaviours associated with drug addiction and some excellent examples can be used to represent this. For example, rats can be trained to lever press to obtain a drug of abuse and will go on to develop compulsive drug taking behaviour. These models have shown that specific brain circuits are mediators of reward, and recent studies highlight the development of habitual behaviours in response to drug cues, suggesting important learning and memory changes are involved in compulsive drug taking.

Evaluating risk
Work published in 2007[1] which reviewed drug harm based on a 'nine-category matrix of harm' led to legal drugs such as alcohol and tobacco being ranked as being more harmful than illegal drugs, such as cannabis and ecstasy. Without entering into political discussions around this subject, this revised method for categorizing drug harm forms a useful basis for discussion of how legality has little to do with the potential for a drug to cause harm. In fact it is likely that a significant proportion of drug use by schoolchildren is done without any consideration of the level of legality (whether a drug is class C or A), as the driving factor is availability and cost. One important difference between legal and illegal drugs is the understanding of dose. The illicit drug market is uncontrolled so variations in dose occur, and the fact that street drugs are cut with other substances including other psychoactive compounds of greater risk, pose serious risks to users in terms of potential adverse effects. The UK has also recently seen a surge in the use of 'legal highs'. Obviously, schoolchildren will know that these drugs are legal, but strangely they often consider these drugs to be 'safe' alternatives to illicit substances. A surprising outcome of a recent review of the legal high Mephedrone highlighted how little was known about its pharmacology. In fact, very little is actually known about the pharmacology and therefore safety of many legal highs, which is in stark contrast to substances such as amphetamine which were developed and therefore tested as medicinal products. These examples illustrate that legality has little to do with overall harm and the increasing development and marketing of 'legal highs' poses as yet unknown risks to users. Interestingly, a poll on the 'Ask Frank' website (www.talktofrank.com/) asking 'Do you think if a drug is legal, it's likely to be safe?' had recorded ~61,000 votes of which 24% voted yes.

In all aspects of human behaviour we evaluate risk and reward, but drug taking alters this process because of the ability of the drug to powerfully stimulate the reward system and thus drive drug taking behaviour. Emphasizing longer term risks, such as addiction and the harmful effects induced by chronic drug taking (e.g liver damage) from excess alcohol ingestion, can be an important educational message but often one that individuals find difficult to fully appreciate. A lack of symptoms can make people believe they are not affected. It is obvious that symptoms might only be apparent once damage is done, but schoolchildren find it difficult to make this connection. A key educational message is that the desire to take drugs (the craving) is a very powerful consequence of drug taking and that this overrides rational thought and action so all other activities are lost in the constant cycle of drug seeking and drug taking. **Why is this so important?** Because once addiction has developed it is very difficult to treat. A person might believe it will not happen to them, may believe they are in control, but they probably do not realize that at a biological level drugs of abuse can take control of their behaviour. As human beings we might think we are always in control.But we, particularly as teenagers, fail to understand that drugs of abuse target biological processes that can drive drug taking behaviour to the detriment of other aspects of life. It might be useful to re-evaluate the types of information given to schoolchildren about drugs of abuse with less emphasis on what drugs look like, how they are administered, and street costs, and more emphasis on their pharmacology, risk and addiction.

Reference
1. Nutt DJ, King LA, Saulsbury W, Blakemore C. Development of a rational scale to assess the harm of drugs of potential misuse. The Lancet 2007; 369: 1047 - 1053.

Cognitive enhancers:
a 'smart' choice?

Nikolas Dietis and Thomas Longden

Nikolas Dietis, University of Leicester

Thomas Longden, University of Manchester

Nikolas is a research student (Ph.D.) at the University of Leicester, Department of Cardiovascular Sciences and a Doctoral Students' Representative to the Departmental Academic Committee. His main scientific interests include opioid pharmacology and the effect of opioid receptor dimerisation on drug action Nikolas is a member of the British Pharmacology Society, Society for Neuroscience and the Greek Pharmacological Society.

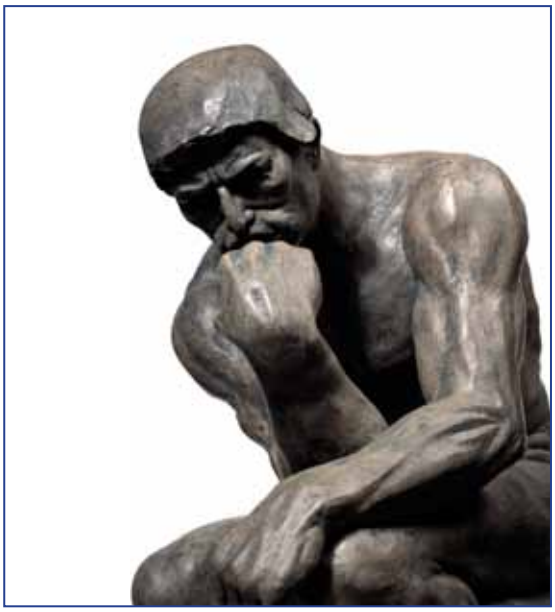
Thomas has just finished his PhD in Pharmacology at the University of Manchester, where he also undertook his undergraduate degree. Thomas is about to move to the US to begin a postdoc and is an active member of the Young Pharmacologists Committee.

Tom and Nikolas both won the BPS Schachter award this year, the award supported their postgraduate visits to the University of Vermont and the University of Modena respectively.

"My heart wasn't beating any faster. I was just able to glide into a state of concentration – deep, cool, effortless concentration. It was like I had opened a window in my brain and all the stuffy air had seeped out, to be replaced by a calm breeze... That night, I lay in bed, and I couldn't sleep. I wasn't restless or tetchy; I just kept thinking very clearly, and I wanted to write it all down... The next morning I woke up and felt immediately alert. Normally it takes a coffee and an hour to kick-start my brain; today I'm ready to go from the second I rise. And so it continues like this, for five days: I inhale books and exhale articles effortlessly. My friends all say I seem more contemplative, less rushed – which is odd, because I'm doing more than normal."

This is how Johann Hari, an award-winning journalist from Glasgow, describes his experience of modafinil, a widely abused nootropic (from Greek nous: mind, trepin: to turn). Johann's experience, which is just one of many similar descriptions that can be found on the web, almost sounds too good to be true: a drug that can make your mind sharper, restless to absorb any amount of information, without any apparent side-effects. Indeed, some users of nootropics (also known as 'smart drugs') have reported a remarkable ability to concentrate and remain awake for extended periods of time (up to 48 hours) without side-effects or having to pay back a 'sleep debt' afterwards.

"But is this all true? What is the catch? Where do I get it from?" These are the first questions that one might come across when surfing web forums,



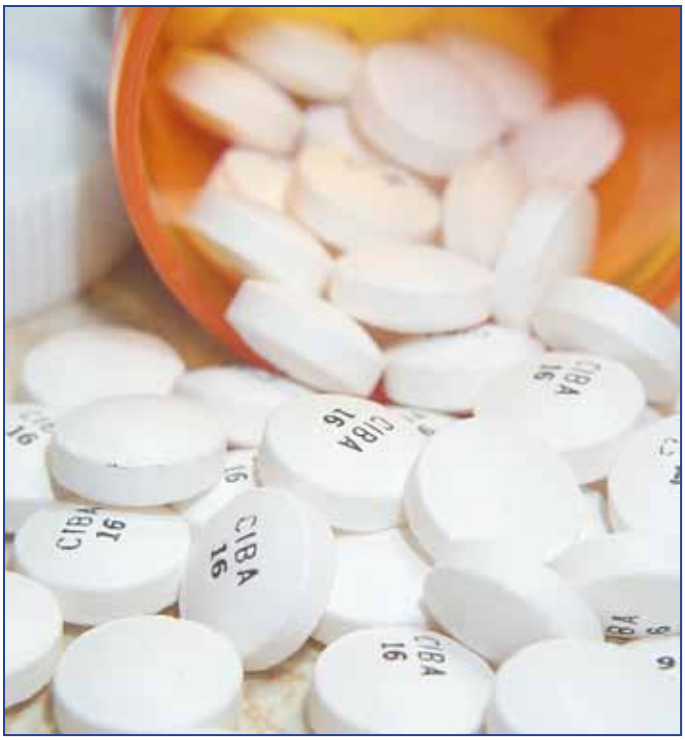
"I was just able to glide into a state of concentration – deep, cool, effortless concentration."

from people who feel the need to enhance their natural mental abilities. However, before rushing to obtain their own illicit supply of smart drugs, prospective users should be aware of the potential dangers associated with these drugs.

Although neuroscience has made impressive steps in the last decade into previously unknown areas and our understanding of the basic mechanisms underlying cognition and memory are rapidly advancing, the brain is still by far the most mysterious organ in the human body. The countless millions of intricate neuronal circuits linked together by synapses form a very complex environment. In such an exquisitely poised and delicate system, the abuse (overuse) and misuse (use for non-therapeutic aims) of nootropics and stimulant drugs is potentially very dangerous.

However, a number of drugs that are used to treat a broad range of CNS diseases, including Alzheimer's, Parkinson's, narcolepsy and attention deficit hyperactivity disorder (ADHD) are seeing increasing 'off label' use in healthy people for cognitive enhancement. Perhaps unsurprisingly there is little data in the literature from controlled studies on the effects of these drugs in healthy subjects, and their mechanisms of action are often poorly understood. Drugs including modafinil (which is clinically used to treat narcolepsy) and methylphenidate (more commonly known as Ritalin or Provigil and used to treat ADHD) are thought to either promote the release or prevent the reuptake of neurotransmitters, such as dopamine and noradrenaline, in the synaptic cleft and thereby potentiate their action.

Other classes of drugs that seemingly enhance neuronal stimulation and increase the workload that the brain can handle include the acetylcholinesterase inhibitors (e.g. donepezil, a drug used to treat Alzheimer's disease) and AMPA



Ritalin SR 20mg

receptor agonists (e.g. memantine, also used for Alzheimer's). A derivative of the inhibitory neurotransmitter GABA, named piracetam (used to treat a broad range of neurological problems), can also act as a cognition enhancer and is thought to do so by opening various ion channels to increase neuronal excitability, whilst at the same time increasing brain blood-flow. Although we appreciate, albeit not fully, how these drugs exert their effects, more research is needed to fully understand the exact mechanisms, which will provide vital insights into risks associated with their use. Furthermore, despite rumours that there are no side-effects when using these drugs in healthy subjects, people can and do experience a range of unwanted effects including mood swings, anxiety, restlessness, a sense of detachment, headaches, insomnia, nausea, loss of appetite, depression, psychosis, paranoia, palpitations, increased heart rate, increased blood pressure and even heart attacks. Alarmingly, nothing at all is known about the effects of long-term smart drug abuse and whether this might lead to addiction and serious health problems.

The fact that some users report no side-effects might be partially explained in terms of dosage and time of use: Most abusers or misusers of nootropics, if not all, do not follow a particular dosage regime and therefore the effects vary. Some abusers take these neuroenhancers "when needed" without steady administration over time. Others might unknowingly take an overdose of nootropics due to a lack of proper medical advice. Clearly, the use of smart drugs for cognitive enhancement in healthy people is illegal and these drugs should only be taken after prescription by a medical professional. However, many of the drugs described in this article can be bought easily and cheaply from 'online pharmacies' without requiring a prescription. A simple Google search instantly retrieves a wealth of sources from which modafinil and Ritalin can be obtained. A pack of 100 modafinil tablets can be ordered from a US-based online pharmacy for just £55. Worryingly, the content of the drugs ordered from these outlets cannot be guaranteed, meaning that users risk inadvertently ingesting unknown and dangerous mixes.

Whilst raising awareness of the potential health dangers associated with the abuse of smart drugs is of paramount importance, it is also important that the ethical considerations arising from the use of smart drugs in schools and universities, in the workplace and even in sports are considered. In a survey conducted at the University of Michigan, 8% of undergraduate students admitted to illegally using prescription drugs to improve their mental performance. Why is this? It may be because students are simply looking for an easy solution to avoid hard work, or perhaps they feel forced into taking such drastic action due to the pressure to perform well in their studies? Should such use be considered 'mental doping'? If viewed in this way, the increasing abuse of smart drugs could have implications for the way that schools and universities monitor and assess learning. Furthermore, if in the future smart drugs were deemed safe by the relevant authorities and their use for cognitive enhancement was made legal, could we arrive at a situation where employees are being put under pressure to take drugs to enhance their work performance? It is important that such questions are addressed as research into these drugs continues.

Due to the lack of properly controlled, thorough clinical research into both the short- and long-term effects of smart drugs, it is important that awareness is raised in users as to the potential dangers associated with this form of drug abuse until more information is available. However, one cannot rule out the prospect of a safe pharmacological intervention for cognitive enhancement and learning augmentation in the future. An eventuality that, perhaps, we should now be prepared for.

'Mephedrone' (*4-methylmethcathinone*): what is it, how commonly is it used and what are the risks associated with its use?

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Background

Towards the end of 2009 and throughout 2010, there has been increasing media interest in the novel recreational drug known as 'mephedrone'. Additionally, over this time there has been increasing evidence of harm associated with mephedrone use, leading to its control under the UK Misuse of Drugs Act (1971) on 16 April 2010. In this article, we will briefly outline what mephedrone is, the patterns of mephedrone use and summarise the available evidence on the harm associated with its use.

What is mephedrone?

Mephedrone is a synthetic cathinone and is the common name for the chemical compound 4-methylmethcathinone. Other synthetic cathinones that are used recreationally include methedrone, methylone and methylenedioxypyrovalerone (MDPV). The synthetic cathinones have similar names to each other and to other non-cathinone drugs, such as methadone, which has led to some confusion. Additionally, there are numerous 'street names' for mephedrone, such as 'miaow miaow', 'plant food', 'bubbles', and 'MCAT'. These are used by not only those selling and using mephedrone, but also by the media. The use of these street names has led to confusion amongst some users who mistakenly believed that all 'plant food' products produce similar desired effects to mephedrone.

Mephedrone is supplied to users as a powder, tablets pressed from powder, or capsules containing the powder. Self-reports and qualitative studies suggest that it is used predominantly by either oral ingestion or by nasal insufflation (snorting). It is uncommon to use mephedrone by other routes, similar to that for other recreational drugs.

Where does mephedrone come from?

The majority of mephedrone sold and used in Europe appears to be manufactured by 'research

A survey of just over 1000 school and college/university students showed that one in five of those surveyed reported previous use of mephedrone

chemical suppliers' in China and neighbouring South East Asian countries. Users may be able to source mephedrone directly from these chemical suppliers, typically in large bulk quantities.

When it was legal to sell and possess mephedrone, the majority of the supply in the UK was through either internet suppliers or from high street 'head shops'1, although increasingly there is evidence of supply of mephedrone through street level drug dealers. The majority of internet suppliers selling mephedrone were based in the UK. Although the majority of users would purchase in small quantities from these suppliers, often significant discounts were available for large (kilogram) purchases. Products were typically sold as 'not for human consumption', but they often included cryptic information to users such as the dose for 'an adult plant' or 'a 70kg plant'. Other information, such as the actual constituents of the products and potential unwanted effects, was often not made available to users.

There has been no published data to date demonstrating the effect of the change in the UK legislation on mephedrone use and supply. Anecdotal evidence suggests that mephedrone use continues to be widespread. There is no information as to where individuals are currently sourcing mephedrone from, now that it is controlled. Potential sources include supply from: i) mephedrone bulk purchased / stock-piled prior to the 16 April 2010 legislation; ii) internet suppliers in the UK and elsewhere; and iii) 'street level' drug dealers. Interestingly, since the change in the UK legislation in April 2010, there appears to have been a decrease in the number of internet suppliers that are based in the UK. However, internet suppliers based outside of the UK continue to offer users the opportunity to purchase mephedrone for shipping to the UK. Although non-UK based suppliers would not be subject to UK legislation, typically they do not advise those purchasing mephedrone that they would be in possession of a classified / illegal substance.

Pharmacology of mephedrone
Mephedrone is a synthetic ring-substituted cathinone, and as such is closely related to the phenethylamine family of recreational drugs. The main difference in its chemical structure relates to the keto functional group at the beta-carbon. It was first synthesized in 1929, and there are several published well described methods of mephedrone synthesis. Despite this, there is very limited information relating to pharmacokinetic and pharmacodynamic effects of mephedrone in both animal models and humans.

From a pharmacokinetic perspective, the limited information available comes from user self-reports, although these are unsubstantiated with no toxicological screening to confirm mephedrone use. These reports suggest that the onset, in relation to absorption and distribution, of 'desired' effects occurs a few minutes following nasal insuffulation and 15-45 minutes after oral ingestion (with some delay if food is present in the stomach). The duration of desired effects, in relation to mephedrone metabolism and excretion, appears to be 2-3 hours following use. The potential metabolites of mephedrone have reported in a rat model, although the time course of detection of these metabolites and their relative proportions was not described.

To date, there have been no published animal models reporting the pharmacodynamics of mephedrone. Human data on the pharmacodynamics of mephedrone is again available from user discussion forums. The desired effects related to mephedrone from these self-reports include euphoria, general stimulation, enhanced music appreciation, elevated mood, decreased hostility, improved mental function and mild sexual stimulation. These are similar to that seen with other stimulant (sympathomimetic) drugs such as cocaine and MDMA (3,4-methylenedioxymethamphetamine). Further data on the pharmacodynamics of mephedrone is available from reports of mephedrone toxicity - these are summarized in the section on toxicity below.

How common is mephedrone use?
Data on the use of established recreational drugs in the UK is collected annually through the British Crime Survey. Data on mephedrone has not, to date, been collected in these surveys; although mephedrone is likely to be included in future surveys. This is unlikely to capture the true prevalence of mephedrone use as this survey only captures data on those aged 15-59. Therefore, it will not collect data on those outside of this age range, which is of relevance as previous media coverage suggested mephedrone use in younger teenagers and schoolchildren.

Sub-population group data collected in 2009 and 2010 suggests that there was a high prevalence of use amongst certain groups such as 'clubbers' and students. In a survey of approximately 2000 UK clubbers in 2009, 41.7% reported that they had tried mephedrone and 33.6% reported having used it within the last month. Mephedrone use within the last month was comparable to that of established recreational drugs (e.g. cocaine 47.4%, ecstasy 48.4%). A survey of just over 1000 school and college/university students in 2010 showed that one in five of those surveyed reported previous use of mephedrone, with the youngest user being aged 12 years.

What harms are associated with mephedrone use?
Information on the acute harm (toxicity) associated with the use of mephedrone has been published in a number of case series from ourselves in the UK, from the National Poisons Information Service in the UK, as well as from other groups elsewhere in Europe. Individuals with toxicity related to self-reported mephedrone use typically develop sympathomimetic features, such as dilated pupils, anxiety/agitation, tachycardia and hypertension. Other severe sympathomimetic features of toxicity, such as chest pain, hypertension, arrhythmias and seizures, have occurred in a small but clinically significant minority of individuals. These features of acute mephedrone-related harm are similar to those reported by users in internet discussion forums and/or qualitative studies. However, it should be noted that currently information on the acute toxicological profile of mephedrone is limited to a few hundred cases, and therefore it is possible that other uncommon, but clinically significant, severe effects associated with mephedrone use have not yet been reported. For example mephedrone-related hyper-pyrexia, seen with other stimulant (sympathomimetic) recreational drugs, has not been encountered, this may reflect that the majority of cases reported have been from months when the ambient air temperature is low and therefore significant hyper-pyrexia is less common.

There are limited reports on user internet discussion forums that high dose and/or frequent use of mephedrone, can be associated with significant 'craving' for mephedrone. Additionally, there are anecdotal reports of 'mephedrone dependency' in qualitative user surveys and from a small number of drug treatment agencies in Europe. There is no animal model of mephedrone dependence liability and no human studies looking at this potential systematically.

Finally, there has been widespread media coverage, particularly in the UK, on deaths where mephedrone use has been implicated. These media reports typically occur around the time of the death, when detailed toxicological screening has not been undertaken to confirm whether mephedrone

was directly implicated in the cause of the death. There is some suggestion that these media reports may have actually increased public awareness of mephedrone and therefore its use. To date, there have been a small number of deaths where mephedrone has been detected in post mortem toxicological screening, and of these cases, mephedrone has been the cause of death in only a small proportion.

Summary
Mephedrone is a synthetic cathinone which is being used recreationally for its stimulant (sympathomimetic) effects and properties. There is increasing published information and data on the acute harms, including death, associated with mephedrone use, and the potential for dependence in some users. Whilst mephedrone, and related cathinones, were controlled in the UK on the 16 April 2010, the effects of this legislation on the supply and use of mephedrone has not yet been established.

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Cannabis and cannabinoids:

pharmacology, medicalization and recreational use

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- *the discovery of endocannabinoids and the endocannabinoid system;*
- *the recent discovery that ethanolamides formed from omega-3 polyunsaturated fatty acids seem to be endocannabinoids;*
- *the gathering of evidence supporting cannabinoids for the management of multiple sclerosis;*
- *the discovery that tetrahydrocannabivarin (THCV) is a phytocannabinoid;*
- *the pharmacological characterization of certain phytocannabinoids and of novel synthetic cannabinoids, e.g. the phytocannabinoids THCV, cannabidiol and cannabigerol, the first water-soluble cannabinoid (O-1057), the first CB1 receptor-selective agonists (e.g. methanandamide), and a widely-used CB2 receptor antagonist (AM630);*
- *the discovery of a cannabinoid CB1 receptor allosteric site;*
- *the development of cannabinoid bioassays, some widely used (e.g. the "ring test").*

See also www.abdn.ac.uk/ims/staff/details.php?id=rgp

Discovery of Δ9-tetrahydrocannabinol

Cannabis has been used as a medicine, for religious ceremonies and recreationally for over 5000 years. Indeed, an alcohol-containing tincture of cannabis (Figure 1) was a licensed medicine in the UK until its withdrawal in the early 1970's. In contrast, the discovery that cannabis contains (-)-trans-Δ9-tetrahydrocannabinol (Δ9-THC) and that many of the effects experienced when cannabis is taken recreationally are caused by this 'phytocannabinoid' was made less than 100 years ago (Pertwee, 2006). These effects include altered mood (usually euphoria); altered perception such that colours seem brighter, music more pleasant and 'felt time' appears to pass more slowly than 'clock time'; an increased desire for sweet food (the 'munchies'); changes in thought processes; impaired memory...and eventual drowsiness. They can also include increased heart rate, a lowering of blood pressure resulting in dizziness and, at high doses, hallucinations and feelings of paranoia. There is good evidence too that Δ9-THC targets the reward centres of the brain in a manner that can lead to psychological dependence, and that abrupt termination of repeated use of cannabis or Δ9-THC can trigger a transient physical withdrawal syndrome that in abstaining recreational cannabis users most commonly includes disturbed sleep, reduced appetite, restlessness, irritability, sweating, chills, a feverish feeling and nausea.

Some cannabinoid pharmacology

The discovery of Δ9-THC was followed by the development of synthetic compounds capable of inducing Δ9-THC-like effects. Results obtained from pharmacological research with some of these compounds culminated in the discovery that they produce many of their central effects by activating specific sites on nerve terminals called cannabinoid CB1 receptors in a manner that influences the normal functioning of the brain (Pertwee, 2006). This finding prompted a search for molecules within our own bodies that can activate these receptors and, in 1992, led to a second major discovery - that we do indeed produce and release such molecules. The first of these 'endocannabinoids' to be identified was an ethanolamide of the omega-6 unsaturated fatty acid, arachidonic acid. It was named 'anandamide', ananda being the Sanskrit word for internal bliss. It has subsequently emerged that there is at least one other cannabinoid receptor (CB2), that there are other endocannabinoids, and that this 'endocannabinoid system' of receptors and endogenous receptor activators plays major roles in the control of our health and in ameliorating unwanted symptoms such as pain.

The search is now on for additional cannabinoid receptors and endocannabinoids. Indeed, we have obtained evidence that ethanolamides, which are converted in our bodies from omega-3 polyunsaturated fatty acids that are found, for example, in fish oil, can both activate cannabinoid receptors and attack cancer cells (Brown et al., 2010).

The medicalization of cannabinoids

Individual cannabinoids first entered the clinic in the 1980's (Crowther et al., 2010). The first of these was Nabilone (Cesamet), a synthetic Δ9-THC-like compound that is used to suppress nausea and vomiting produced by cancer chemotherapy. Synthetic Δ9-THC (Marinol) was licensed soon after Nabilone for the same purpose, and subsequently as an appetite stimulant, particularly for AIDS patients. Nabilone and Marinol were recently joined in the clinic by Sativex: in Canada (2005) for the relief of multiple sclerosis and cancer pain and in the UK (2010) to treat spasticity due to multiple sclerosis. Sativex has also received regulatory authorisation in Spain. Its main constituents are two phytocannabinoids, Δ9-THC and cannabidiol, both extracted from cannabis.

Figure 1. Tincture of cannabis.

Importantly, whereas exogenously administered cannabis and individual cannabinoids such as Δ9-THC and Nabilone target all cannabinoid receptors in the body and so 'flood' the whole endocannabinoid system, endocannabinoids released endogenously are somewhat more selective since they seem to be released in a manner that only targets subpopulations of their receptors. Although such release is often 'autoprotective' it can sometimes be 'autoimpairing', leading for example to CB1 receptor-mediated obesity. There is, however, currently little interest in developing medicines from compounds that block CB1 receptors, as such a blockade could well also suppress CB1 receptor-mediated autoprotection. Indeed, the CB1 receptor blocking drug, Rimonabant, was recently withdrawn from the clinic because of an increased incidence of depression and suicidality in patients taking it as an anti-obesity agent.

The fact that Cesamet, Marinol and Sativex are all in the clinic is of course an indication that, as prescribed, these medicines do significantly more good than harm. Even so, there is considerable interest in developing a second generation of cannabinoid medicines that display even greater 'benefit-to-risk ratios' (Pertwee, 2009). Possibilities include compounds that avoid the production of unwanted cannabinoid CB1 receptor-mediated effects by:

(1) Only activating cannabinoid receptors that are located outside the brain and spinal cord.

(2) Only activating cannabinoid receptors in particular tissues such as skin or spinal cord by being administered directly into these tissues.

(3) Activating cannabinoid CB2 but not cannabinoid CB1 receptors.

(4) Being administered at low doses that produce a cannabinoid receptor-mediated enhancement of the sought-after effects of non-cannabinoid medicines but are insufficient to produce significant cannabinoid receptor-mediated unwanted side effects.

(5) Boosting the levels of endocannabinoids when these are being released in an 'autoprotective' manner, for example to relieve pain.

(6) Targeting 'allosteric' sites that we have discovered to be present on cannabinoid CB1 receptors in a manner that will boost the ability of autoprotectively released endocannabinoids to activate these receptors.

Cannabis: a complex scenario

Δ9-THC is synthesized in the cannabis plant from a non-psychoactive precursor, Δ9-THC acid. This process can be greatly accelerated by heat which is why cannabis is usually smoked, often with tobacco, consumed in preheated food or inhaled from 'volcano' vaporizers that create fumes by heating cannabis without burning it or producing smoke. Other pharmacologically active phytocannabinoids can also be formed from their acids by heating cannabis. These include the non-psychoactive yet pharmacologically active compounds, cannabidiol (CBD), Δ9-tetrahydrocannabivarin (Δ9-THCV) and cannabigerol (CBG), each of which has actual (CBD) or potential medical applications. Some of these phytocannabinoids are really 'fighto' cannabinoids, their presence in cannabis making it a pharmacological 'battlefield'. Thus we have discovered that although CB1 receptors are activated by Δ9-THC, they can be blocked by Δ9-THCV. It has also been found that CBD can oppose certain effects produced by cannabis or Δ9-THC. Indeed, whilst there is evidence that the presence of Δ9-THC in cannabis increases the risk of developing schizophrenia for certain individuals, there is also strong evidence that cannabidiol is a potential medicine for the treatment of schizophrenia. A further complication is that the relative concentrations of different phytocannabinoids are not the same in all strains of cannabis, in all parts of the same cannabis plant or in male and female cannabis plants, the female flowering heads of sinsemilla ('without seeds') being particularly rich in Δ9-THC. This may have important consequences for those who take cannabis either recreationally or for the quite different purpose of self-medication, as high CBD:THC or THCV:THC ratios may lessen the risk from cannabis of developing schizophrenia or cannabis dependence...although probably also alter the perceived nature of a cannabis-induced 'high'.

Spice

One notable recent event has been the arrival in the recreational cannabis world of herbal mixtures laced with synthetic cannabinoids ('designer drugs') such as JWH-018 (e.g. Spice or K2, named after the second highest mountain on earth). These little-investigated synthetic cannabinoids share the ability of Δ9-THC to activate cannabinoid CB1 receptors and hence to produce a 'high'. Moreover, any of them that activate these receptors more stongly than Δ9-THC will most likely produce a more intense 'high' and perhaps also more serious unwanted effects than usually experienced by recreational cannabis users. They probably also differ from THC in other ways. Thus, although Δ9-THC shares its ability to target cannabinoid receptors with many synthetic compounds, the additional pharmacological actions it possesses provide it with a unique 'pharmacological fingerprint' that distinguishes it from many of these other compounds.

Harm minimization for recreational cannabis

One important challenge for the International Narcotics Control Board that monitors and implements United Nations

drug control conventions is to select an optimal but workable strategy for minimizing the harm that is now being caused both to themselves and to Society by some of the many millions of people worldwide who currently take cannabis (or Spice) recreationally and also, indeed, by some of those who self-medicate with 'street' cannabis. For the UK, options include leaving the present law unchanged, increasing or decreasing current penalties for the supply and/or possession of 'street' cannabis, and legalizing cannabis either unconditionally or in a manner that, for example, (i) does not permit cannabis to be taken by adolescents or other individuals who are thought to be at particular risk from cannabis-induced harm and (ii) makes available legal material that (a) contains approved combinations and levels of cannabinoids and (b) can be taken as an inhaled unburnt vapour or in other ways that avoid the lung damage caused by smoked cannabis. It will be important that policy makers have discussions with cannabinoid pharmacologists whilst considering these and any other potential strategies for minimizing the harm caused by recreational cannabis.

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Alcohol: the Need for a Solution

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Hilary is Professor of Addiction Science at the Institute of Psychiatry. After obtaining her degrees (BSc, MSc and PhD) at Manchester University, she worked as a postdoctoral researcher in the Pharmacology Department at Oxford University, and was subsequently appointed to a staff position in that department, where she remained until 1986. Hilary then joined the Department of Pharmacology, Bristol University, as a Wellcome Trust Lecturer, and continued in that department as Wellcome Trust Senior Lecturer, University Senior Lecturer and then Reader. In 1995 she became Professor of Psychopharmacology in the Psychology Department at Durham University, then in 2002 moved to St George's, University of London, as Professor of Addiction Science until 2009.

Hilary's research work has primarily centred around drugs of dependence, initially, working on psychostmulants and then mechanisms of general anaesthesia. This was followed by studies on drugs acting on benzodiazepine receptors and the formulation of the two way benzodiazepine receptor theory. She then moved to alcohol dependence research, which has been her focus ever since. Hilary uses a multidisciplinary approach, applying coordinated behavioural, neurochemical, and electrophysiological techniques to investigate neuronal mechanisms underlying behavioural changes. Her current specific areas are the development of pharmacological treatments for alcohol dependence, in particular drugs that block calcium channels and the glucocorticoid antagonists, the long term influence of stress in alcohol dependence, and the effects of chronic alcohol consumption on memory.

Acute actions of alcohol

In countries in which its sale is legal, alcohol is used by around 90% of the adult population, some only occasionally, some on a daily basis. It is frequently, however, not regarded as a 'drug'. In a social context, the lack of scientific basis for the legal classification of drugs has recently been highlighted (1). Alcohol and nicotine are legally available over European and American continents, but cause considerably greater health problems than illicit drugs. In a scientific context, little attention has been paid until recently to the pharmacology of alcohol. In fact, experimental problems have even been caused when alcohol is used as a solvent for other drugs, as some scientists occasionally overlook the fact that alcohol not only has substantial pharmacological effects itself but it may interact with the drugs under study.

The effects of alcohol have been described as "non-specific", a term which is frequently misinterpreted as meaning non-selective, but the term non-specific is used here in the precise pharmacological sense, to indicate that alcohol is not acting via specific binding sites on receptor proteins. It does not mean that alcohol is non-selective in its actions: in fact, at low concentrations, the effects of alcohol on synaptic transmission in the brain are very selective (2). Alcohol has been described both as a 'stimulant' and as a 'depressant', but neither description is either useful or scientifically accurate. At low doses alcohol can have excitant "disinhibitory" effects. As the dose ingested rises, alcohol has more of an overall depressant effect on the CNS. The widely-used phrase "loss of inhibition" does not refer to the effects on central synaptic transmission, but rather that alcohol has euphoric and anxiolytic properties that can result in relaxation of the normal constraints on behaviour.

Acute pharmacological actions of alcohol

Many direct and indirect effects are caused by alcohol on different transmitter systems but the important ones are those that are produced at blood concentrations which are found in the body when alcohol is consumed. At high doses, alcohol is a general anaesthetic, and was used for many years for this purpose. Alcohol acts at millimolar concentrations, considerably higher than those at which most drugs are effective (see Table 1).

Acutely, alcohol decreases the effects of excitatory neurotransmitters, such as glutamate (see Table 1). Activation

of endogenous opiate transmission by alcohol has been found to occur at relatively low concentrations and is thought to be involved in its euphoric effects. Alcohol has a range of acute effects on monoamine transmission, in particular, activating the mesolimbic dopamine system (see below) and affecting 5-HT (serotonin) pathways, including potentiation of the activation of 5-HT3 receptors. Alcohol also increases the actions of the inhibitory transmitter GABA (gamma-aminobutyric acid), but this is not apparent on all neurones which use GABA as a transmitter, nor in all areas of the brain.

Alcohol dependence

Alcohol dependence is a major health problem, which costs the NHS around £3billion per year (3) and has immense social and economic costs. Not everyone who drinks becomes dependent, there is much clinical and preclinical evidence to suggest that both experience (such as stressful situations) and genetics play an important role in the development of dependence. Adolescent drinking is a risk factor for the development of dependence and it is thought that dependence involves synaptic plasticity, i.e. changes in the strength of neuronal transmission. During adolescence, the brain areas particularly affected by alcohol - the prefrontal cortex and the hippocampus are still developing and this may be why adolescent drinking is so hazardous. The stages of alcohol dependence are illustrated in Figure 1. Frequently, alcoholics stop drinking, recover from the acute withdrawal syndrome and manage weeks or months of abstinence, but then start drinking again (i.e. relapse drinking).

Acute alcohol withdrawal is a serious condition that can involve fatal convulsions but it is relatively easy to treat. Benzodiazepine drugs are normally used for this, and they prevent the immediate symptoms, but do not affect the underlying dependence and do not reduce relapse drinking. We know a considerable amount about the neuronal basis of the acute alcohol withdrawal syndrome. Excitatory amino acid transmission is facilitated and increased movement of calcium ions into neurones has been demonstrated. These changes can cause neurotoxicity, and it is thought that they, combined with the raised glucocorticoid levels during the acute phase of withdrawal, may be responsible for the neuronal damage and cognitive deficits suffered by alcoholics. The mesolimbic dopamine system in the brain is involved in "reward" processes and the reinforcing effects of drugs, although its exact role is uncertain. Alcohol has activating effects on this system, as do most other drugs that cause dependence, but the precise neuronal basis of the compulsion to drink high, risky, amounts of alcohol is not yet fully understood.

Over all the available treatments, relapse drinking rates in the long term are 70 to 90%, so more effective treatments are urgently needed. Recent studies have shown persistent symptoms, including sleep problems, anxiety and depression. These have now been recognized to be a "protracted withdrawal syndrome" and there is some evidence that the severity of these correlates with the likelihood of relapse drinking, but it is still very difficult to predict which patients will manage to maintain abstinence.

Pharmacological treatments for alcohol dependence

The development of pharmacological treatments for alcohol dependence is many years behind the development of drugs that are effective in treating other mental disorders,

primarily because of how drug dependence has previously been regarded. Until only 20 - 30 years ago it was thought that dependence was due simply to lack of will-power and it was not considered to be a disease at all, never mind one that could be treated with other drugs. During the 1980s,

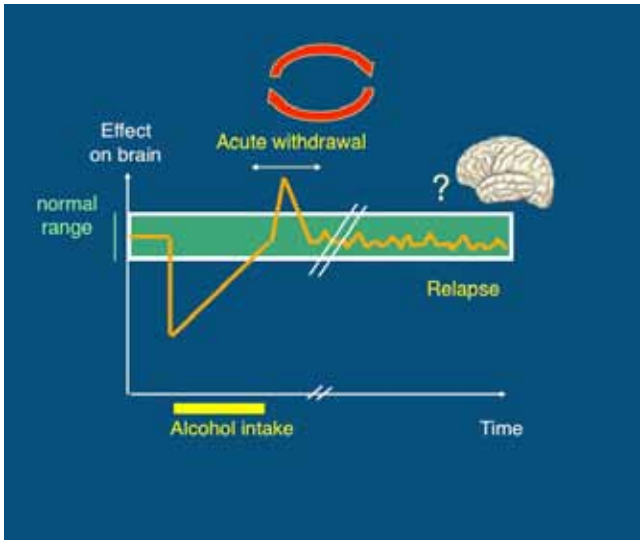

Figure 1: Progress of the effects of alcohol. This figure is a diagrammatic representation of the changes in the effects of alcohol over long time periods. During the first phase, tolerance develops. When alcohol drinking stops the acute withdrawal syndrome appears, this is then followed by an abstinence phase. During abstinence, relapse drinking frequently occurs resulting in cycles of withdrawal and relapse.

my colleagues and I, working in the field of basic alcohol research (in those days we were an extremely small band!), were told by both the MRC and the Wellcome Trust that they "did not fund" research on alcohol dependence. Things have changed immensely since then, with the MRC making drug dependence a target area since the 1990s, but considering the magnitude of the health problems caused by alcohol, academic investment is still extremely small. The attitude of the pharmaceutical industry has been even slower to change, somewhat surprisingly considering the size of the potential market for effective drugs, but there is now at last more interest in this area.

The breakthrough in the acceptance of pharmacological treatments for alcohol dependence came with two drugs, naltrexone and acamprosate. Naltrexone was well established as an antagonist of opiate receptors, blocking the effects of the opiate class of drugs that includes morphine and heroin. During the 1980s however, it was discovered that this drug reduced alcohol consumption by rodents, and clinical trials have shown its effectiveness (4). The mechanism of action of acamprosate is not yet understood but this drug has shown effectiveness in clinical trials (5). The reduction in the rates of relapse drinking by these drugs is only around 10 - 20% but they have shown that pharmacological treatment can provide some improvement. Further studies are needed, and some are in progress, to find more effective drugs (see Table 2).

Another aspect that has hindered the development of pharmacological treatments for alcohol dependence has been difficulties in studying compulsion to drink'. Some strains of rats and mice like alcohol and will drink a lot of it, while others will hardly touch it unless they have nothing else to drink, and there is now a large field of study of the genomic basis of this. Operant methodology, involving lever pressing, has been considered to model how much 'work' an animal is willing to perform in order to obtain alcohol,. Whilst drugs with promising effects on drinking behaviour have been found (see Table 2), correlations with the effects in humans are not yet good enough, suggesting that the experimental models need to be improved. Inclusion of the important aspect that a human dependent on alcohol, or other drug, continues to ingest it despite knowing that it will cause serious them harm, would have beneficial consequences.

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Table 1 Concentrations of alcohol at which the acute effects are produced.
The first set of concentrations (*In vivo*) are examples of plasma concentrations in humans measured during the actions of alcohol. The second set (In vitro) are examples of the concentrations of alcohol in the perfusion or culture medium during studies on isolated neurones.

(i) *In vivo* (plasma concentrations)		
Mild intoxication in humans	5 - 20 mM	23 - 92 mg%
Sedation, motor inco-ordination in humans	20 - 50 mM	9
General anaesthesia in humans	50 - 100 mM	230 - 460 mg%
Legal driving limit in the UK	17.4 mM	80 mg%
(ii) In vitro		
Depression of NMDA-receptor mediated depolarisations (Lovinger, 1989)	5 to 50 mM	23 - 230 mg%
Reduction in AMPA/kainate receptor mediated depolarisations (Martin et al., 1995)	25 - 100 mM	115 - 460 mg%
Reduction of calcium currents (Mullikin-Kilpatrick and Treistman, 1994)	5 to 50 mM	23 - 230 mg%
Potentiation of 5-HT3 receptor effects (Lovinger, 1991)	25 - 100 mM	115 - 460 mg%
Increased firing of dopaminergic ventral tegmental neurones (Brodie et al., 1990)	20 - 320 mM	92 - 1472 mg%
Potentiation of effects of GABA (Takada et al., 1989)	70 mM	322 mg%
Facilitation of effects of endogenous opiates (Xiao et al., 2007)	20 - 80 mM	92 - 368 mg%

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Table 2. Examples of putative future drug treatments for alcohol dependence.

\+ overall positive effects in studies
++ substantial positive effects
0 no overall positive effect in studies
? not yet tested

Drugs	Reduction of alcohol consumption in rodents	Reduction of acute alcohol withdrawal syndrome	Clinical prevention of relapse drinking
Topiramate (anticonvulsant)	+	++	+
Carbamazepine (anticonvulsant)	+	++	+
Baclofen (agonist at $GABA_B$ receptors)	++	+	+/0
Dihydropyridine calcium channel blockers	++	++	?
Gabapentin	+	++	+
Endocannabinoid receptor (CB_1) antagonists	+	+	+
Selective serotonin reuptake inhibitors	+	0	0
Blockade of Type II glucocorticoid receptors	+ (stress-induced drinking only)	+	?
Decreased glucocorticoid synthesis	+	+	?
Corticotrophin releasing factor receptor antagonists	+ (only after chronic alcohol ingestion)	+	?

Profile:

Medical Research Council Short Course in Translational Pharmacology participant

David Sweeney, University of Leicester

Earlier in the year, BPS hosted a residential course in Translational Pharmacology at King's College London. Translational Pharmacology had been identified by the Medical Research Council (MRC) as a strategic gap in research training and this course was a pilot developed to address this issue. The course was funded by an MRC grant awarded to course organisers Professor Sue Brain, Dr Jude Hall and Dr Mark Christie with BPS as the administering organization.

Mr David Sweeney, (PhD student, Department of Cell Physiology and Pharmacology, University of Leicester), attended the week-long course and comments here on his experience. Interview by Dr Jude Hall

What is your academic background?
I had always been interested in chemistry and biology at school, and particularly in the science behind understanding how drugs work - pharmacology, but did not continue my studies beyond A-level. Rather, I started my working life working as a telecommunications IT project manager in the civil service, where I stayed for 12 years. After this time an opportunity arose to switch careers, I immediately applied to do a degree in science at my local university, the University of Bedfordshire. I chose to study a BSc joint honours degree in Biochemistry and Pharmacology, after 3 years of hard work I left with a 1st class degree. I then chose to further my knowledge and practical skills by completing on a MSc in Molecular Medicine at Cranfield University in Bedfordshire. After this I was sure that I wanted to pursue a career in the field of drug discovery, which brings me to my current position as a PhD student at the University of Leicester. I chose my PhD because of its translational nature: I am researching the hypothesis that calcium homeostasis in airway smooth muscle cells taken from asthma patients is different to those from normal healthy volunteers. This project allows me to gain experience of modern pharmacological techniques both at the bench and using epifluoresence widefield and confocal microscopes as well as having an appreciation and understanding of the clinical aspects of respiratory disease; indeed my two supervisors ensure this, a Professor of Pharmacology and a Professor of Respiratory Medicine and Senior Wellcome Clinical Fellow.

What is your connection to the Medical Research Council?
My PhD is funded for four years by the MRC, currently I am in my 3rd year.

How did you find out about the short course?
By e-mail from the MRC.

How were participants selected?
Participants were asked to send a CV and a letter to explain why they should be given a place on the course. Clearly this was going to be a tough selection process with many worthy candidates applying. I was sure that I had a strong case, my PhD is designed around translational principles since my lab work is guided by clinical relevance, so I set about writing, and re-writing several times, a clear case to be selected for the course. It was a nervous wait before I finally got confirmation that I had been selected to be on the course. I think that this is actually one of the keys to this course's success - many people just apply to go on courses - turn up and do not contribute or find it not to their liking, for this course only those candidates with a positive and active interest in translational pharmacology were selected. For me an additional bonus was that the course would have a day devoted to respiratory pharmacology which was very relevant to my PhD project on asthma.

Can you describe the course?
The course consisted of lectures followed by 'breakout' seminar sessions then further lectures or activities such as a visit to a nearby clinical trials unit. The course organization was excellent, the lectures were delivered by experts in their each specialist area of translational medicine, with a good mix of enthusiastic people from industry and academia; each lecture held everyone's interest and not a minute was wasted, the speakers were recognized experts in their field, and the information imparted was up to date and top quality. The breakout sessions were a chance to consolidate the material introduced during the lectures and a chance to ask the speakers questions. The course itself builds on your working knowledge of pharmacology, particularly receptor theory, and led us into the world of drug discovery at a fairly brisk pace and intensity. The course was progressive and logical with one concept building on a previous one so the overall effect was a deep understanding of real world translational pharmacology.

What are your overall feelings about the course? Was it a worthwhile experience?
Overall the course provided me with a confident foundation knowledge in this subject area over a week that was not boring, and full of chances to ask questions and interact with others, it is surprising how this interaction can help you clarify your own research questions and problems. The course was well resourced with a part of the BPS website ('Moodle VLE') providing materials for study prior to the course. As well as the teaching quality being particularly high the organization of the social and domestic areas was also particularly pleasing. We stayed at a convenient hotel which was a rather pleasant walk across Waterloo Bridge from the venue. Throughout the day we were amply served with refreshments I thoroughly enjoyed the final evening meal which the delegates and most of the speakers attended.

This was a great chance to socialise and a great way of rounding off the course. I thought the course was great and the organization was a big part of this success. Thanks to the whole course team, Amalie and Jude in particular for their presence ensuring that we were happy with the progress of the course, and generally keeping everything flowing smoothly throughout the week.

Has attending the course impacted on your career aspirations? In particular, did you learn more about the role research councils such as MRC and learned societies such as BPS can have in career development?
I am very grateful to the MRC and BPS as their reputation had obviously attracted the best speakers and delegates to the course. I have personally gained tremendous benefit from speaking to those at the top of their fields and believe that other delegates who were PhD students like myself or postdocs that had come to refresh their knowledge would have learnt a lot too. I am now positive that I would like to pursue a career in drug discovery, this had always been my goal but this course has confirmed this for me, and given me impetus to pursue my goal after my PhD. I was so impressed with the professionalism of the BPS and its obvious importance amongst my peers that I have now become a member of BPS and am actively looking at other opportunities offered by the MRC and BPS in my career portfolio. I would thoroughly recommend this course to any pharmacologist that feels they would like to enter the drug discovery arena but are not sure.

This course will give you a taste of what it is like to be at the top of this fascinating and essential part of medicine.

News from the Young Pharmacologists

Sara Barnes, Young Pharmacologists' Editor

I ♥ Pharmacology: Social Events

The Young Pharmacologists kicked off their first social event of 2010 at the WorldPharma 2010 conference in July. Held in the beautiful Danish capital of Copenhagen, 45 young pharmacologists from countries all around the world got together for a speed networking event in the Old Town's vibrant New Harbour district. With the BPS buying the first round of drinks, the evening got off to a good start, and continued to get more lively as participants rotated around the room discussing ice-breaker questions such as 'Industry or academia?' and 'Football or Opera?' with their international colleagues. A fun evening was had by all involved! Notably, the eagerly anticipated I ♥ Pharmacology T-shirts made their first appearance, elegantly modeled by the BPS pharmacologists hosting the event: Oliver Keown, Tom Longden, Liz Rosethorne and Karen Schlaegel.

More I ♥ Pharmacology T-shirts will be available as prizes at the next Young Pharmcologists' social event in December, during the BPS Winter Meeting, London 2010. Come and meet other young life scientists on Tuesday 14 December 2010 onboard The Tattershall Castle, a former paddle steamer permanently moored on the River Thames that has been converted into a stylish bar. Including a buffet and entertainment, tickets are a bargain at only £5 for BPS student members and £10 for everyone else. Tickets can be booked when registering for the BPS Winter Meeting online, and with places limited you should book now to avoid disappointment!

BPS 2010 Winter Meeting: Lipid Symposium and Undergraduate Bursaries

Besides the fantastic evening social event onboard the Tattershall Castle, the Young Pharmacologists' committee has also organized a symposium at the upcoming BPS 2010 Winter Meeting (14-16 December). Entitled Pharmacology of Lipid Mediators in Health and Disease, this half-day symposium will examine the roles of lipid mediators in the immune, respiratory and cardiovascular systems as well as the receptors and cell signaling pathways that underlie these functions. Featuring an introductory lecture by Professor Rod Flower FRS, this symposium promises to be a stimulating and exciting addition to the scientific programme. We look forward to seeing you there!

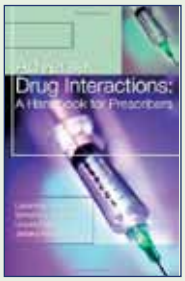
The Young Pharmacologists Committee again offered 30 bursaries of up to £200 towards travel, accommodation and poster production to undergraduates who wanted to present a poster at the BPS Winter Meeting, London 2010. Even though the posters won't be formally assessed, we would like to encourage all attendees to support our undergraduate bursary winners.

Old and New Members of the Young Pharmacologists' Committee

Many thanks to Lydia Staniaszek, Tom Longden, Annie Geraghty and Rhiannon Thompson who are stepping down after serving for several years on the Young Pharmacologists' committee. Their hard work and dedication have been responsible for making the committee as active as it is today - thanks guys! We are delighted to welcome four new members to the team: Nikolas Dietis (Leicester), Louis Dron (Leicester), Daniel Reed (Imperial) and Hannah Watson (Edinburgh).

The eagerly anticipated I ♥ Pharmacology T-shirts made their first appearance

Book reviews:
Adverse Drug Interactions: A Handbook for Prescribers



Adverse Drug Interactions: A Handbook for Prescribers

L Karalliedde, SFJ Clarke, U Collignon, J Karalliedde

Hodder Arnold, 2010, pp. 771. ISBN 9780340927694

Drug-drug interactions occur when two drugs are co-administered, and one (the precipitant drug) alters the pharmacokinetics or pharmacodynamics of the other (the object drug). This can increase or reduce the effects of the object drug, causing either adverse effects or failure of therapy. Erythromycin inhibits the metabolism of warfarin; bleeding can result. Enzyme inducing drugs, such as phenytoin, carbamazepine, and rifampicin, increase the clearance of oestrogens; this can cause failed oral contraception.

The numbers of reported adverse drug interactions increases year on year. The pace of increase can be roughly judged from the number of pages devoted to drug-drug interactions in the *British National Formulary* (BNF) (Figure 1). Between issue 1 (1981) and issue 46 (2003) there was a linear five-fold relative increase from about 1% of the total book (4 pages) to 5.4% (45 pages), while the book itself increased in size only about two-fold (from 387 to 836 pages). There was then a sharp increase to 8.5%, partly due to a small change in font size and the inclusion of some extra information. Since then there has been no further significant change, although the absolute number of pages devoted to interactions has increased from 74 (issue 47) to 89 (issue 59), while the book has grown in total proportionately.

Drug-drug interactions (of which about 6000 are listed in the latest issue of the BNF) pose several problems for prescribers, since adverse effects that occur as a result are in principle preventable. First, prescribers need to know whether an interaction has been described. Secondly, whether that interaction is likely to cause a serious adverse effect. Thirdly, what to do about it. The BNF currently divides interactions into two types—those that it says are "potentially hazardous … where combined administration of the drugs involved should be **avoided** (or only undertaken with caution and appropriate monitoring)", and those that are not so designated and which can presumably be ignored. This dichotomous classification leaves something to be desired, since it is hard for the prescriber to know what course of action (complete avoidance or use with monitoring) to take when there is a risk of serious harm, although in some cases advice is given. Furthermore, there is no guidance about what type and frequency of monitoring is needed nor about the cases in which a change in dosage of the object drug is required.

There is no guidance, for example, in the BNF on what to do if you have to advise a patient who is taking warfarin about the use of paracetamol. The text says "prolonged regular use of

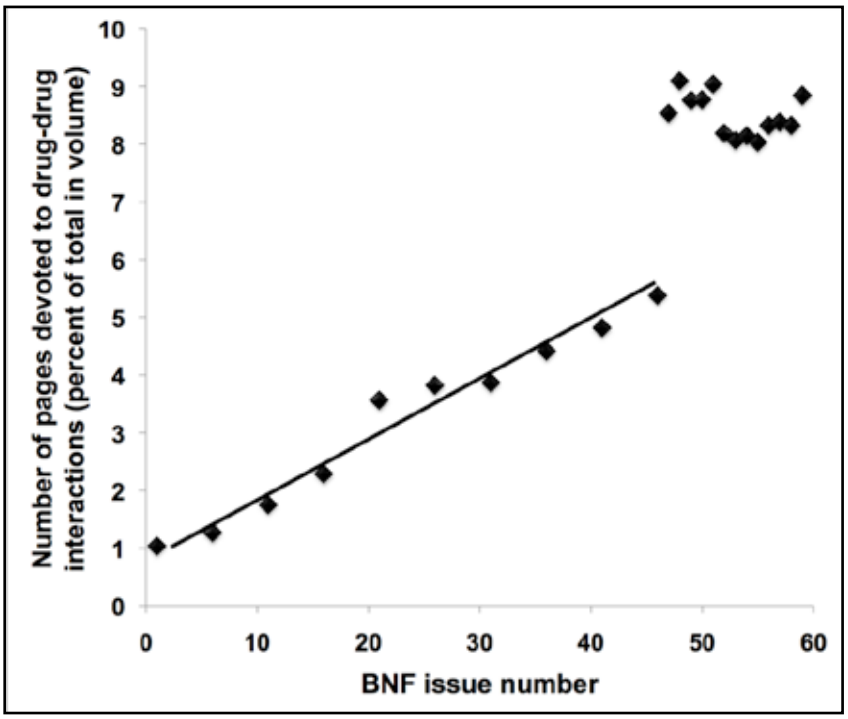


Figure 1. The numbers of pages devoted to drug-drug interactions in issues of the BNF since issue 1 (1981) (percent of the total number of pages in each issue)

paracetamol possibly enhances anticoagulant effect of coumarins", but the interaction is not marked as being "potentially hazardous". I believe that this underestimates the importance of this interaction; I have seen several patients with severe bleeding and an International Normalized Ratio (INR) over 15 (reference range 0.8–1.2) after they had taken regular paracetamol for a few days, with no other factors to blame. And a persuasive case-control study has shown that after a few days of regular use paracetamol potentiates the effect of warfarin: the more you take for longer, the bigger the effect [1]. The mechanism may be pharmacodynamic [2], perhaps via an action on factor VII [3]. So, one would advise a patient taking warfarin that paracetamol can be used occasionally, but should not be taken regularly, or at least not for more than a day or two.

This example illustrates some of the difficulties. **Does this new text help?** Unfortunately not, on several counts. First, it is difficult to find the information, even if you know what you are looking for. There is no cross-index to tell you that, for example, the interaction of warfarin with thyroid hormones is described on page 399, the last of 10 pages devoted to oral anticoagulants, which you therefore have to search one by one, and there is no entry for "thyroid hormones" in the index. Earlier in the section we learn that the anticoagulant effect of oral anticoagulants is possibly increased when paracetamol is taken regularly (but not occasionally), but we are not told what "regularly" means; the text reports that the mechanism is "uncertain" but may be inhibition of warfarin metabolism (for which there is no good evidence), and advises monitoring the INR "closely" for the first 1-2 weeks of starting or stopping regular paracetamol. Slightly better than the BNF but still not adequate.

Stockley's Drug Interactions, available on line through "Medicines Complete" [4], is usually a good source of information, particularly since it gives references to the primary literature and advice about what to do. However, on this occasion it gets it wrong: "an interaction between paracetamol and the coumarins is not firmly established ... it is not possible to firmly recommend increased monitoring, or dismiss its advisability." This advice is based on randomized studies, and the case-control study is played down. However, there are occasions on which, despite the views of the evidence-based medicine movement, observational studies are more reliable than randomized trials. In this case, the risk of confounding in the case-control study was minimized by the fact that all the other factors that one would expect to be associated with an increased effect of warfarin were demonstrated, and by a convincing dose relation. Furthermore, the randomized studies have been small and may have failed to detect an interaction that possibly occurs only in susceptible individuals. For example, in one study only 11 patients were included [5]; such a study could have missed an important effect if only 30% of subjects were susceptible. In another study, in 20 patients, the mean INR rose rapidly after the start of paracetamol therapy and was significantly increased within 1 week compared with placebo [6]. The rise could have caused bleeding in some patients, and this small study could have missed a larger effect if only 15% of subjects were susceptible. In such a case the precautionary principle applies.

Another problem arises from interactions that involve a drug with all or some of a group of drugs. For example, clozapine should not be used in combination with anticancer drugs because of an increased risk of neutropenia. This interaction is listed by Karalliedde et al. under "Antipsychotics" and "Anticancer and immunomodulating drugs", but I had difficulty finding it, even though I knew what I was looking for. Had I wanted to know if there was an interaction of clozapine with a specific anticancer drug, say carmustine, I could not have found out—that interaction is not mentioned under either "antipsychotic drugs" or "carmustine". The same is true for all other anticancer drugs. In the BNF, this interaction is mentioned under each anticancer drug separately, as it should be.

If you are a UK prescriber and want to know about a drug-drug interaction, I suggest that you start with the BNF, where you will find out whether it occurs and, if so, whether you need to take notice of it. If you want extra information, you can look in Stockley. However, this is still not ideal. Take the interaction of pentoxifylline with ketorolac: in the BNF it is marked with a bullet and the advice "avoid concomitant use"; Stockley, on the other hand, says "The UK manufacturer, rather cautiously, contraindicates concurrent use, whereas the US manufacturer made no mention of this tentative interaction."

A more concerted approach to this problem is required, summarizing the risks and the quality of the evidence [7].

Jeff Aronson, Reader in Clinical Pharmacology, University of Oxford

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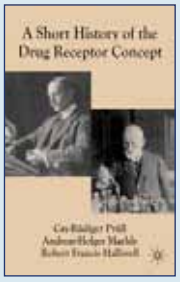
A Short History Of The Drug Receptor Concept



A Short History Of The Drug Receptor Concept

Cay-Rudiger Prull, Andres-Holger Maehle, Robert Francis Halliwell

Palgrave Macmillan, 2009, ISBN 9780230554153

The central tenet of pharmacology is that many drugs exert their agonist or antagonist effects by interactions with receptors. Furthermore, the different physiological effects of drugs are explained by the specific classes of receptors with which each individual drug interacts. This is the subject of our textbooks, and most biological scientists and all clinicians are exposed to these fundamental concepts of drug action. Thus, pharmacology would not be recognizable without the central concept of the receptor. But it may not have been this way. The fascinating history of the development of the drug receptor concept is the subject of this well-written book authored by Prull, Maehle and Halliwell. For a short history it is packed with details and written in an engaging style that provides social and political contexts not normally encountered in most scientific accounts of the subject. Sections can be re-read with different information becoming apparent on each reading.

It is well documented that Ehrlich developed the idea of a receptor through the context of immunology and that Langley introduced the idea of receptive substances in cells in the context of physiology. This book also documents the use by Ehrlich of the lock and key metaphor, his love of novels, and his propensity to befriend his colleagues while strongly defending his theories from any criticism.

Importantly, the receptor concept was in contrast to the idea that the physicochemical properties were important determinants of the actions of drugs. This view was strongly advocated by influential representatives of academic pharmacology such as Straub in Germany and Cushny in England. As is generally known, it was through the work of Clark, Gaddum, and Stephenson (among others) that the receptor theory we recognize today was elaborated. Even then, the concept of receptor subtypes was not recognized for several decades.

Receptor subtype selectivity is the central idea driving drug development. Compounds are generated and screened on the basis of interactions with specific subtypes and the more specific the fewer expected side effects. This is the basis for research in pharmacology and related disciplines and for the pharmaceutical industry, a major generator of economic activity around the world. This book explains that it took over a decade from when the idea was first proposed by Ahlquist to the concept being used. Indeed, the idea was at first rejected and Ahlquist had difficulties in getting his work published in the pharmacology literature. From a modern day perspective, this appears absurd and the book's treatment of this subject is particularly informative. Ahlquist encountered the problem that his novel explanation for the differential effects of adrenalin on specific pharmacological responses was due to adrenalin acting on different subtypes of receptors contradicted a theory proposed by the prominent physiologist, Cannon. The work by Cannon on the role of adrenalin in the response to stress was pioneering and made him an influential figure. Cannon also went on to explain the differential responses of adrenalin by its actions on a single receptor that subsequently released from cells different mediators, Sympathin E (excitatory) and Sympathin I (inhibitory). The editors of the Journal of Pharmacology and Experimental Therapeutics rejected Ahlquist's data and interpretation in favor of the dominant theory and appear to have served their field poorly. Ironically, modern pharmacology was restored by the editor of the American Journal of Physiology who published Ahlquist's pioneering work. It is evident from this and other examples that protecting the status quo is the antithesis of scientific journals, which serve as a repository of new knowledge. The authors state: "The decision making of editorial boards ….is often guided not only by the quality of the research concerned but also by considerations of its political and strategic relevance and its relationship to dominant scientific theories or paradigms. This is still true in our time." Indeed it is. For example, the field of behavioural pharmacology/neuropharmacology has been ceded to psychologists whose central theories are incompatible with those of pharmacology. The historical perspective of this book illuminates well this important lesson.

For a book entitled "A Short History…" it covers key aspects of the subject in some depth and in an entertaining and informative manner. This is must reading for students in their third year of undergraduate training in Europe and similar systems and for second year graduate students in the US and Canadian systems. It should be mandatory reading for the editorial boards of major pharmacology journals and others entrusted with disseminating the information that advances our chosen field. The insight offered by this well-documented treatise presents important lessons for all of us and offers an informative perspective on how our field evolved to its present day structure.

Professor Andrew B. Norman, University of Cincinnati.

BRITISH PHARMACOLOGICAL SOCIETY

Today's science, tomorrow's medicines

About the BPS

With almost 2,700 members, the British Pharmacological Society (BPS) is the primary learned society in the UK concerned with research into drugs and the way they work. Its members teach and carry out research in higher education, the pharmaceutical and biotechnology industries, hospitals, and health services. Many members play a key role in teaching medical students the principles of pharmacology, which underpin safe and effective prescribing in the NHS. Others are responsible for the clinical trials that translate new medicines from molecule to society.

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For Pharmacologists and Clinical Pharmacologists.

Standard Tariff - £90

Associate Member

Open to individuals having a professional interest in pharmacology or a closely related subject who do not have the necessary qualifications to become Members.
Standard Tariff - £60

Postgraduate Member

Open to individuals studying for higher degrees in pharmacology, or closely related subjects. Also open to clinicians in training who have a specific interest, or intend to follow a career in clinical pharmacology.

Standard Tariff - £20

Undergraduate Member

Open to individuals studying for degrees in pharmacology and other undergraduates whose courses include a substantial pharmacology component. Also open to medical students at any stage of training.

Standard Tariff - £5 (One off fee during undergraduate studies)

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Benefits

- free attendance to BPS scientific meetings including the Winter Meeting to be held in London in December
- enjoy access to the full online versions of the British Journal of Pharmacology and British Journal of Clinical Pharmacology
- become eligible for bursaries and travel grants to attend meetings in the UK and overseas
- apply for prestigious study awards and prizes such as the A J Clark Studentships and GSK Prize for Young Investigators
- receive regular editions of Pharmacology Matters, the BPS newsletter
- opportunities to contribute to furthering pharmacology, across a range of activities, through the Society's committees, special interest groups and working parties

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