Commentary: Addiction potential of medicinal drugs

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Much material in SD805 addresses the issue of 'what is addiction?', but in order to examine the pharmacological issues, the first question to answer is 'what is a drug?'

You will know that in everyday conversation, the word 'drugs' (often used in the plural when meant in the singular) is frequently used to refer exclusively to drugs being taken illegally. Furthermore, psychologists often use the term with an implicit understanding that they are referring to drugs that can alter behaviour. Depending on the context, medical/healthcare workers use the term to refer to either drugs used for therapy (medicinal drugs) or illegally used drugs of abuse. Pharmacologists, on the other hand, take an all-embracing view of drugs. They use the term to describe any molecule that produces a biological effect on living tissue. Such molecules are regarded as drugs regardless of their legal status, usage, abuse potential, or target system (e.g. cardiovascular, digestive, etc.). Crucially, pharmacologists include in their thinking the many hundreds of potential medicinal drugs that, at any one time, are in development.

Reverting to the material already included in the course, you may have noted that virtually all of the drugs of addiction that have been mentioned have either been used by people for many centuries (e.g. alcohol, nicotine, morphine and cocaine), or are drugs that came into use no later than the 1960s (e.g. benzodiazepines, amphetamines and barbiturates). Important exceptions to this generalization are derivatives of these relatively old drugs. Common knowledge, however, tells us that since the 1960s enormous strides have been made in the pharmacology of the central nervous system (CNS), and highly effective medicinal products have been successfully introduced for treating, or alleviating, conditions such as schizophrenia, depression, anxiety, Alzheimer's disease, Parkinson's disease, sleep disorders and migraine. Although some of these newer products can cause rebound effects on withdrawal, and with the proviso that exceptions can always occur, overall these products have little propensity for causing addiction.

This low propensity for causing addiction is no accident and is the result of many factors. First, in the light of whatever knowledge is available at the time, new drug molecules are often specifically designed with the intention of avoiding the potential for addiction. Second, early in the development of all CNS drugs, animal studies are undertaken that are designed to detect any with the propensity to cause addiction, so that they can be 'filtered' out at an early stage. Pharmacologists believe that, by using a pragmatic approach, this can be done without too much difficulty. They take the view that when you strip away psychological and sociological issues (by using animals), and when dosage levels and dosage regimes are determined by experimenters, those drugs that are likely to cause dependence will show tolerance and/or withdrawal symptoms in animal studies. Several experimental models using different administration routes will be needed, and the phenomena may not be evident in every study.

Mostly, the animal studies involve repeated administration of the drug to laboratory animals (usually rodents) and monitoring for signs of tolerance or withdrawal syndromes.

Typically, a positive control is included in the study, and the effects of the test drug are compared with the positive, and sometimes a negative, controls. A good example is:

> Malmberg, A. B. and Yaksh, T. L. (1995) Effect of continuous intrathecal infusion of omega-conopeptides, N-type calcium-channel blockers, on behaviour and antinociception in the formalin and hot-plate tests in rats, *Pain*, **60**(1), pp. 83–90.

Amongst the experiments reported in this paper are comparisons between SNX-111 (also known as ziconotide) and morphine. SNX-111 induced little or no tolerance in animals, and the findings were subsequently confirmed in other studies. Following successful completion of animal trials, the drug proceeded to clinical trials where tolerance and withdrawal potential were again monitored. A large number of clinical trials now confirm that SNX-111 has a powerful and highly significant analgesic effect against chronic and severe pain (Staats *et al*., 2004). It is expected that SNX-111 (ziconotide) will be launched for general medical use in the near future.

Staats, P., Yearwood, T., Charapata, S., Presley, R., Wallace, M., Byas-Smith, M., Fisher, R., Bryce, D., Mangieri, E., Luther, R., Mayo, M., McGuire, D. and Ellis, D. (2004) Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial, *Journal of the American Medical Association*, **291**(1), pp. 63–70.

As well as reporting experimental findings, this paper by Malmberg and Yaksh, cited above, refers to the mechanisms responsible for the actions and tolerance produced by opiates, and is a good source of references for reading on these topics. [*Minor point*: note that drugs are given reference numbers when first synthesized, e.g. SNX-111. If a new drug starts to look promising, it will be given a name (its generic name, e.g. ziconotide. Brand names are manufacturer- and sometimes country-specific, and are chosen much later.]

Receptor theory and dependence

A quick reminder, and extension, of the concepts of drug action at receptors covered earlier in the course may be helpful at this stage. The pioneer of microbiological chemotherapy, Paul Ehrlich, helped to introduce the concept of drug receptors when he commented: 'Bodies are inactive unless affixed'. The essential feature of action at receptors is that when the normal physiological agent (the natural *ligand*) makes contact with the receptor, there is some biological outcome (e.g. change in membrane potential, opening of an ion channel, etc.). The *effector* (e.g. an enzyme) bringing about the outcome is often said to be *coupled* to the receptor. Most natural ligands have a high *affinity* for the receptor, which means their conformation allows them to fit and bond well with the chemical moieties that form the receptor site. By definition, the natural ligand is an *agonist* even if the outcome is a rather negative in physiological terms (e.g. membrane stabilization). An agent that stops the natural ligand from achieving its intentions is an *antagonist*. It may have a similar, greater or smaller affinity for the receptor site than the natural ligand, and in chemical terms it may bond reversibly or irreversibly with the receptor site. Partial agonists are another type of agent. These have affinity, but do not produce the same maximum effect (lower *efficacy*) as the natural ligand. They block access to the receptor by the natural ligand. To add to the complexity, most receptors come in different types and these types often have subtypes, so there can be a further issue of *selectivity* for receptor types and subtypes.

To illustrate how a series of closely related molecules can be found to have different spectra of (beneficial) biological properties, and different propensities for causing addiction, we can look at the benzodiazepine drugs. This drug class is used medicinally to reduce anxiety, to induce sleep, to induce a unique form of amnesic anaesthesia, to relax skeletal muscle and to prevent or halt convulsions. Unfortunately, those class members with good anxiolytic and hypnotic properties tend to induce dependence. The following papers both serve as illustrations of studies involving different benzodiazepines having different actions at the same neurochemical receptor type (the GABA-A receptor):

Longone, P., Impagnatiello, F., Guidotti, A. and Costa, E. (1996) Reversible modification of GABA-A receptor subunit mRNA expression during tolerance to diazepam-induced cognition dysfunction, *Neuropharmacology*, **35**(9-10), pp. 1465–1473.

Serra, M., Ghiani, C.A., Motzo, C., Porceddu, M. L. and Biggio, G. (1995) Antagonism of isoniazid-induced convulsions by abercarnil in mice tolerant to diazepam, *Pharmacology, Biochemistry and Behavior*, **52**(2), pp. 249–254.

Unless you have a special interest, it may be sufficient to read just one of these papers. Nevertheless, even those readers who are reluctant to probe the technicalities of drug–receptor interactions should try to take away from these papers one central message. This is that the addiction potential of a molecule can be changed by structural changes that alter interactions between the molecule and its receptor sites.

Those who wish to delve further into receptor studies will find plenty of material in the papers by Longone *et al.* and Serra *et al.*, and the further paper given below:

Harris, R. A., Mihic, S. J. and Valenzuela, C. F. (1998) Alcohol and benzo-diazepines: recent mechanistic studies, *Drug and Alcohol Dependence*, **51**(1-2), pp. 155–164.

This paper by Harris *et al.* draws attention to the similarities in actions of benzodiazepines and alcohol, and contains some material that may look rather formidable to those without a biochemical background. It is, though, well worth reading in order to get an overview, if not the detail, of the issues that are regarded as important. At this stage, it may be helpful to be aware that benzodiazepines and related compounds produce most of their pharmacological effects by *allosterically* positively modulating GABA-A receptors. What this means is that the benzodiazepines act at a spatially distinct site on the GABA-A receptor, which is close to the active site. When benzodiazepines attach themselves, they alter the consequences of the approach of the neurotransmitter GABA to the active site. The effect is enhancement of action, hence *positive modulation*.

One attempt at distinguishing between different benzodiazepines has been on the basis of their different actions at GABA-A receptors, and they can be divided into *full allosteric modulators* (FAMs), *selective allosteric modulators* (SAMs) and *partial allosteric modulators* (PAMs) on the basis of *efficacy*, *affinity* and *selectivity*. The compounds compared in the papers by Longone *et al.* and Serra *et al.* include diazepam (a FAM), imidazoline (a PAM) and abercarnil (a SAM).

Towards the end of the paper by Harris *et al.* (in Section 4, on p. 161) there is a brief mention of the existence of different types of benzodiazepine drug with different specificities, as described above.

Receptor theory in relation to investigation and management of dependency

The next three key papers are mostly concerned with known drugs of addiction. Although they have each been chosen to represent a different pharmacological aspect of drug addiction, they share a focus on events at receptor sites. The first of these papers is also the core paper.

Childress, A. R. and O'Brien, C. P. (2000) Dopamine receptor partial agonists could address the duality of cocaine craving, *Trends in Pharmacological Sciences*, **21**, pp. 6–9.

This paper pursues the idea of partial agonists as possible aids in the treatment of cocaine craving, and presents a clear review of the therapeutic potential of this type of drug. The paper includes a review of data concerning a drug in development, which might be of a use in the management of cocaine craving.

Ward, J., Hall, W. and Mattick, R. P. (1999) Role of maintenance treatment in opioid dependence, *The Lancet*, **353**(9148), pp. 221–225.

This paper by Ward *et al.* offers a more clinical view of the importance of what happens at drug receptors. No in-depth understanding of receptor theory is needed to follow the thread of this paper. It is a clearly written review of opioid maintenance therapy, focusing especially on treatment with methadone. The essence of this type of therapy is the medicinal use of opioid analogues with a route of administration, duration of action, receptor selectivity and efficacy that differ from morphine and its derivatives (e.g. heroin). Methadone itself is an opiate agonist, and other agents mentioned are either antagonists or partial agonists. Agonism and antagonism at opiate receptors is rendered more complicated by individual drugs having different actions at the muw, delta and kappa opiate receptor sites, but it is the muw site that seems to be the key site so far as opiate dependence is concerned. [*Minor point*: note that the paper adopts the normal convention for scientific and good clinical journals and uses generic names for drugs (e.g. buprenorphine and naltrexone), not the brand names (e.g. Subutex and Nalorex).]

Volkow, N. D., Wang, G-J., Fowler, J. S., Logan, J., Gatley, S. J., Gifford, A., Hitzemann, R., Ding, Y-S. and Pappas, N. (1999) Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels, *American Journal of Psychiatry*, **156**(9), pp. 1440–1443.

This paper by Volkow *et al.* is included because it is typical of studies that can now be undertaken in humans, by looking at the number of receptors in selected brain areas. Using positron emission

tomography the study examined inter-subject variability in receptor levels, and compared this with mood changes following administration of the dopamine re-uptake system blocker, methylphenidate. Receptors were labelled by the binding of an isotopically labelled ligand ([^{11}C]raclopride), which binds *competitively* and *selectively* to dopamine D_2 and D_3 receptors. Put another way, raclopride has selective affinity for the receptors, and competes with dopamine for access to the receptor sites.

The parameters and indices used by Volkow *et al.* are explained in more detail in the second of the two papers listed below by the same authors, which includes a study in which competitive displacement of [^{11}C]raclopride by endogenous dopamine is used to assess the amount of dopamine released under conditions where the dopamine re-uptake system is in rendered inactive.

Concluding remarks

In a short section such as this, only a limited number of concepts can be covered. However, the fundamental issues described are applicable to all drug actions and hence all drug addictions. Amongst the topics omitted are nicotine dependency, and the prospects for developing 'vaccines' that prevent addictive drugs implementing their actions. Papers covering these two topics are included in the list of supporting articles below, where an outline of the theme of each paper is included in square brackets. As well as being interesting in their own right, these supporting papers provide a starting point for any future literature search.

Supporting articles

Carrera, M. R. A., Ashley, J. A., Parsons, L. H., Wirsching, P., Koob, G. F. and Janda, K. (1995) Suppression of psychoactive effects of cocaine by active immunization, *Nature*, **378**, pp. 727–730. [Active immunization against cocaine suppresses cocaine-induced locomotor activity and stereotyped behaviour in rats.]

Kreek, M. J. (2001), Drug addictions: molecular and cellular endpoints, *Annals of the New York Academy of Sciences*, **937**, pp. 27–49.

Kreek, M. J., LaFroge, K. S. and Butelman, E. (2002) Pharmacotherapy of Addictions, *Nature Reviews Drug Discovery*, **1**(9), pp. 710–726.

Nestler, E. J. and Aghajanian, G. K. (1997) Molecular and cellular basis of addiction, *Science*, **278**(3), pp. 58–63. [Includes a review of uncoupling of receptors during addiction.]

Sanchez, C., Arnt, J., Costall, B., Kelly, M. E., Meier, E., Naylor, R. J. and Perregaard, J. (1997) The selective sigma$_2$-ligand Lu 28-179 has potent anxiolytic-like effects in rodents, *Journal of Pharmacology and Experimental Therapeutics*, **288**(3), pp. 1323–1332. [Includes a comparison of test drug with benzodiazepines for anxiolytic effects, tolerance and withdrawal effects.]

Thompson, G. H. and Hunter, D. A. (1998) Nicotine replacement therapy, *Annals of Pharmacotherapy*, **32**(10), pp. 1067–1075. [Includes the theory and practice of nicotine replacement therapy.]

Volkow, N. D., Wang, G–J., Fowler, J. S., Gatley, J., Logan, J., Ding, Y-S., Dewey, S. L., Hitzeman, R., Gifford, A. N. and Pappas, N. R. (1999) Blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of high', *Journal of Pharmacology and Experimental Therapeutics*, **288**(1), pp. 14–20. [Pursues the theme of why methylphenidate induces a 'high', using PET scans with radiolabelled cocaine.]

Volkow, N. D., Wang, G-J., Fowler, J. S., Logan, J., Gatley, J., Wong, C., Hitzemann, R. and Pappas, N. R. (1999) Reinforcing effects of psycho-stimulants in humans are associated with increases in brain dopamine and occupancy of D_2 receptors, *Journal of Pharmacology and Experimental Therapeutics*, **291**(1), pp. 409–415. [Continues the theme, mentioned in the text above, of dopamine receptor occupancy and the effects of psychostimulants.]