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Psychopharmacology – a remarkable development

Psychopharmacology, the study of psychotropics, or brain-mind-altering substances, is a fascinating field at the confluence of neurochemistry and behaviour. Basic psychopharmacologists are mostly interested in how psychotropics work, often studying neurochemical properties of different compounds in animal models. Clinical psychopharmacologists are mainly interested in the clinical applications of psychotropics, often working in psychiatric settings. But what exactly are psychotropics? How in fact do they work? How widely are they used, and do they really help people?

In this chapter I begin by outlining the broad scope of psychopharmacology: emphasizing that psychotropics have been long, widely, and intensively used by humankind for a range of purposes; describing the relatively recent birth of modern psychopharmacology as an empirical science; and noting that despite the remarkable progress in the field to date, psychopharmacology is at an early stage in its development. Then, in the next chapter I go on to consider the major philosophical issues raised by the advent of modern psychopharmacology.

The length, breadth, and depth of psychotropic use

And he drank of the wine, and was drunken; and he was uncovered within his tent. (Genesis 9:21, King James Version)

What is better adapted than the festive use of wine, in the first place to test, and in the second place to train the character of a man, if care be taken in the use of it? (Plato, 1970)

Humans use psychotropic agents in a range of different contexts. We imbibe stimulants such as caffeine as part of our regular diet and to enhance our attention and performance, we celebrate social occasions and perform religious rites with alcohol, we experiment with consciousness-altering drugs, and we take psychiatric medications when we suffer from symptoms such as depression and anxiety. There is no reason to suspect that we have not been engaged in these kinds of activities since the dawn of human time (Moreno, 2006a; Playfair, 1987; Rivers, 2001).

This use of psychotropic agents by *Homo sapiens* is remarkable in a number of different ways. For one thing, reliance on psychotropics is a phenomenon that differentiates humankind from most other species. In the laboratory, a range of animals can certainly become addicted to substances. But in the wild, there is only accidental contact with psychotropics. While there have been occasional reports of non-human primate use of plants for medicinal purposes, such reports have rarely if ever extended to psychotropic agents (Rodriguez *et al.*, 1985; Whiten & Boesch, 2001).

Indeed, in comparison to the use of other pharmaceuticals, human use of psychotropics is remarkable for its broad range. Humans throughout the world have long relied on agents that act on organs such as the gut, the skin, or the heart. However, such pharmaceuticals have invariably been restricted to the prevention or treatment of symptoms of disorders. In contrast, psychotropics have a range of other uses, including as an everyday nutrient and social "lubricant" (spirits), a component of religious rituals and spiritual voyages (entheogens), and performance or cognitive enhancers (nootropics).

The use of psychotropics is also notable for its intensiveness. Ginseng, for example, is a psychotropic herb that played a key role in changing the fortune of Chinese dynasties, due to its high demand and the consequent profits earned from its trade (Taylor, 2006). Alcohol, opium, and cocaine are amongst the addictive substances that have been at the centre of underground battles or international wars, again because each has a substantial market. Modern psychotropic medications have been blockbusters for the pharmaceutical industry, earning it billions of dollars in revenue.

This broad and deep range of uses depends in turn on the complexity of our nervous system – which provides multiple targets for psychotropics to act on, and on the importance of this system to our being – so that psychotropics can have wide-ranging and profound effects. It also reflects the vast range of psychotropics available to our species; psychoactive agents are found in abundance in the plant kingdom (e.g. steroidal hormones are found in yams, monoamine oxidase inhibitors are present in St John's wort, alcohol is obtainable from fermented fruits), and are now also readily synthesized in the laboratory.

Pharmacological agents may in general be the same as endogenous compounds (e.g. insulin for diabetes), may act as agonists or antagonists at particular receptors so augmenting or blocking endogenous processes (e.g. diuretics enhance diuresis), or may have complex stabilizing or destabilizing effects (e.g. anticonvulsants lower seizure threshold). In the case of psychotropics, we have agents that employ each of these possibilities (e.g. exogenous testosterone acts in the same way as endogenous testosterone, selective serotonin reuptake inhibitors enhance serotonergic neurotransmission, alcohol has destabilizing effects on neuronal membranes).

The advent of empirical psychopharmacology

He who had drunk of this potion would not shed tears for a whole day even if his mother and his father were to die, and even if his most beloved son were slaughtered before his eyes. (Homer, *Odyssey*)

Psychopharmacology is an interdisciplinary science in which many techniques and branches of knowledge are brought together. In seeking to modify human behaviour by the use of chemical substances, it lies at the crossroads of the biological sciences and the humanities, because every psychopharmacological problem concerns the relationship between the body and the mind. (Delay, 2006)

The history of psychopharmacology is notable for its length and breadth and depth, but the advent of psychopharmacology as an empirical science is a recent development (Healy, 2002). The term

"psychopharmacology" has been in use since the early twentieth century, and gained currency in the 1950s, at a time when the first randomized controlled trials of psychotropic agents were undertaken (Thullier, 1999).[1] The field grew exponentially thereafter, driven by rapid advances in both basic science (e.g. molecular neurobiology, behavioural pharmacology, synthetic chemistry) and in clinical science (e.g. operational diagnosis, symptom measurement, trials methodology).

First-generation psychotropics were often found serendipitously. For example, the first antipsychotic agent, chlorpromazine, was developed as an anaesthetic; when it was later found to decrease psychotic symptoms, further investigation established that it was a dopamine blocker (Thullier, 1999). Similarly, the first monoamine oxidase inhibitor – a powerful class of antidepressants – was developed as an antituberculous drug. Once again, investigation of the mechanisms of action led to a focus on monoamines in depression.

Whereas these early agents often had multiple actions, affecting different receptors, second-generation agents were specifically developed in order to act on one receptor at a time. A well-known example is fluoxetine, originally marketed as Prozac, a selective serotonin reuptake inhibitor (or SSRI). In contrast to the tricyclic antidepressant agents, which act on serotonin and noradrenaline receptors, as well as on the cholinergic system, fluoxetine primarily affects the serotonin system. Interestingly, recent agents have been specifically engineered to act on more than one receptor system. These potentially offer the advantage of altering the multiple neurotransmitter systems that may be involved in complex disorders.

A number of points can be made about modern psychotropics. First, they cannot be likened to neuronal sledgehammers – fluoxetine acts on the product of a single gene (of the 23 000 odd in the human body). Second, their effects are nevertheless complex – serotonin interacts with multiple other systems, so that fluoxetine eventually affects a

[1] One of the first to use the term "psychopharmacology" was Jean Delay, a pioneering French psychiatrist who testified in the Nuremberg trials and who had a doctorate in philosophy. During the student protests of 1968, strongly influenced by the work of psychiatrists or those using examples from psychiatry (Fanon, Foucault, Goffman, Laing, Marcuse, Szasz), his office was ransacked, and he was forced to resign.

range of neuronal circuits and ultimately thoughts and emotions and behaviours. Most psychotropics can be termed neuromodulators – they act on multiple circuits that spread throughout the brain. Third, the adverse effects of psychotropics are sometimes overstated; for example, while some medications are addicting, antipsychotics and antidepressants are not. Fourth, this does not mean they do not have crucially important side effects – they do.

Progress in psychopharmacology has had an enormous influence on the theory and practice of psychiatry. Indeed, psychiatry is now primarily "biological" in its approach – whereas the field (particularly in the USA) was dominated by psychoanalytic theories and practices in the 1950s, by the end of the twentieth century psychiatric research leaned strongly on the neurosciences, and psychiatric practice relied heavily on psychopharmacological interventions (Luhrmann, 2000; Sabshin, 1990; Shorter, 1998). While psychiatrists continue to be trained in psychotherapy, and optimal prescription of psychotropics requires a rigorous appreciation of the psychodynamics of the patient, the shift in the field has been revolutionary in its extent and impact.

These developments need to be understood not only in terms of the scientific advances allowed by the new psychotropics, but also in more socio-political terms. The pharmaceutical industry has played a key role in developing and marketing psychotropic products (Angell, 2004; Degrandpre, 2006; Healy, 2004; McHenry, 2006; Moynihan & Smith, 2002; Smith, 1991; Starcevic, 2002; Szasz, 2001; Valenstein, 1998). Although much research on psychopharmacology is funded by government sources, such as the National Institutes of Health in the USA, most large, randomized, controlled trials on psychotropics are funded by the industry. Indeed, psychotropics have proven to be particularly profitable pharmaceutical agents; the market for these agents amounts to billions of dollars per annum (IMS Health, 2002). Large amounts of money may be devoted even to niche areas, such as work on psychotropics to enhance performance in the military (Moreno, 2006b).

The relationship between academic psychopharmacology and the pharmaceutical industry has been subjected to a number of critiques. There are, for example, important concerns about the objectivity of

academic researchers who are primarily funded by industry (Angell, 2004; Healy, 2004). Clinicians have in turn been criticized for over-diagnosing and overtreating psychiatric disorders (Horwitz & Wakefield, 2007; Moynihan & Smith, 2002). More radically, an antipsychiatry movement, which questions the scientific validity of psychiatric diagnoses, and is concerned that psychiatric interventions are better understood in terms of the control of social deviance, has criticised the use of "chemical straitjackets" and the marketing of psychotropics as panaceas (Breggin, 1993; Ingleby, 1981; Sedgwick, 1982).

Gains and gaps in psychopharmacology

> The expectations I have formulated some 25 years ago regarding developments in the pharmacotherapy of depression have not, or only to a small extent, materialized. Neither have they been refuted. (van Praag, 2001)

Critiques of psychopharmacology which emphasize the use of medication to control social deviance, and criticize the use of "chemical straitjackets" and the marketing of psychotropics as panaceas, ignore some empirical data. First, the global burden of psychiatric disorder is enormous, with 5 of the 10 most disabling medical disorders comprising neuropsychiatric conditions (Murray & Lopez, 1996), and second, despite their prevalence and associated impairment, severe psychiatric disorders continue to remain relatively underdiagnosed and undertreated in both developed and developing countries (Demyttenaere *et al.*, 2004). Nevertheless, this volume is primarly concerned with potential problems in the widespread use of psychotropic agents for a range of other psychic ills. While there may have been major gains in psychopharmacology, it is important to also understand the significant gaps in this field.

Modern psychopharmacology has on the one hand arguably achieved remarkable successes. The closure of large, long-term psychiatric hospitals – deinstitutionalization – was largely brought about by the success of antipsychotic agents in treating serious psychotic disorders such as schizophrenia and bipolar disorder. Although depression and anxiety

disorders continue to be underdiagnosed and undertreated, there are now effective medications available for many psychiatric conditions. Although not all data are consistent (Helgason *et al.*, 2004), it is possible that decreases in the prevalence of suicide in some developed countries reflect the better diagnosis and pharmacotherapy of depression (Carlsten *et al.*, 2001).

Modern antipsychotics and antidepressants are relatively safe, well-tolerated, and non-addicting, so that many early concerns about the use of psychotropic agents for psychiatric disorders have diminished over time. New psychotropics are introduced only after carefully conducted randomized controlled trials show both safety and efficacy. The pharmaceutical industry is closely regulated by governmental agencies. Advances in basic mechanisms continue to be made, new agents continue to be introduced, and there is no reason not to suspect that future pharmacological interventions will be even more useful than those currently available.

At the same time, there are notable gaps in our knowledge of the brain-mind in general (Sala, 1999), and of psychopharmacology in particular. First, a full appreciation of the mechanisms of action of psychotropics remains a goal for the future. Although we understand a good deal about the receptors at which most psychotropics act, we understand much less about how changes at these receptors translate into further changes "downstream" at the so-called 2nd and 3rd messenger level, and we do not have a complete understanding of how these changes in turn alter systems that underpin cognition and affect.

Furthermore, currently available psychotropics almost all work by changing monoaminergic neurotransmitter systems; despite the introduction of new and useful drugs in recent decades, these continue to work on similar pathways as did the earliest agents. Thus, although many psychopharmacologists are excited about the progress that has occurred, a number have warned against exaggerating what has been achieved (van Praag, 1998). While modern agents may be better tolerated than older ones, the lack of truly innovative new interventions in psychopharmacology is worrisome to many.

An early idea in psychopharmacology was that of "pharmacotherapeutic dissection"; if disorders A and B responded to medication X but

not Y, while disorders C and D responded to medication Y but not to X – then disorders A and B would have nosological and biological overlap with one another, but not with the overlapping disorders C and D (Klein, 1964). Obsessive–compulsive disorder (OCD), for example, responds more robustly to clomipramine, a predominantly serotoninergic reuptake inhibitor, than to desipramine, an agent that is also a tricyclic antidepressant, but that is predominantly a noradrenergic reuptake inhibitor (Zohar *et al.*, 1988). Furthermore, benzodiazepines are useful in certain anxiety disorders, but not in OCD. Analogously, whereas dopamine blockers typically cause sedation in healthy volunteers, they result in a decrease in psychotic symptoms in those with schizophrenia or bipolar disorder, underscoring the boundaries between psychotic disorders and normality.

Nevertheless, this principle has not been entirely productive in more contemporary research; for example, clomipramine is more effective than desipramine not only for a number of conditions that have much in common with obsessive–compulsive disorder (e.g. body dysmorphic disorder), but also for a number of apparently quite unrelated conditions (e.g. premenstrual dysphoric disorder) (Stein, 2001). Conversely, when a medication is effective, we cannot necessarily deduce a great deal about the mechanisms involved in the relevant disorder. It turns out that there is surprisingly little evidence of serotonergic dysfunction per se in OCD. It is possible that a quite different neurochemical system is at fault in OCD, and that serotonergic medications are effective only via their secondary effects on that other system (Stein, 2002). Furthermore, dopamine-releasing agents are not only effective in improving concentrations in patients diagnosed with attention-deficit/hyperactivity disorder (AD/HD), they may be used by ordinary college students or by military personnel to enhance cognitive performance (Chatterjee, 2006; Kadison, 2005; Vastag, 2004), thus raising questions about the validity of AD/HD as a disorder.

In addition to gaps in our understanding of basic mechanisms in psychopharmacology, there are also important lacunae in clinical psychopharmacology. The majority of randomized controlled trials of psychotropics to date have been undertaken in Western adult populations, over the short term, and in tertiary settings. Regulatory authorities

require only a few positive trials for an agent to be released on the market, typically for a single indication (such as major depression). There are comparatively few data on the use of psychotropics in other kinds of populations (e.g. children), over the long term, and in general psychiatric or primary settings (Klein *et al.*, 2002; Wells, 1999). For many psychiatric disorders, should a first-line medication fail, there is surprisingly little evidence on which to base the choice of a second-line medication (Fawcett *et al.*, 1999; Stein *et al.*, 2005).

Thus, while the advent of modern psychopharmacology has been a remarkable development, this is a young field, and much additional empirical basic and clinical research remains to be done (Klein, 1993; Klein *et al.*, 2002). Of particular relevance to the current volume is the gap in empirical research on "off-label" indications for psychotropic medications. Once a psychotropic medication is made available, additional data on safety may become available on the basis of post-marketing surveillance. However, the prescription of psychotropics for non-registered conditions (for example, the prescription of an antidepressant for depression that does not meet criteria for a major depression) may continue on the basis of clinical judgement rather than empirical trials. The lack of data in this area contributes to the difficulty of the philosophical questions raised by modern psychopharmacology, the focus of the next chapter.

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Philosophical questions raised by psychopharmacology

In addition to the many empirical questions that remain for psychopharmacology, the field has raised important philosophical issues for the cognitive and clinical sciences. Philosophy of medicine, philosophy of psychology, and philosophy of cognitive science have only recently begun to address conceptual issues in neuroscience (Bechtel *et al.*, 2001; Bennett & Hacker, 2003; Bickle, 2003; Churchland, 2002; Mishara, 2007), and by and large have ignored the area of clinical psychopharmacology. This volume attempts to begin to address this notable gap in the literature.

A host of philosophical questions are raised by modern psychopharmacology. For the purposes of this volume, these can be divided into (1) conceptual or metaphysical questions about categories relevant to psychopharmacology, (2) explanatory or epistemological questions addressing our knowledge of how psychotropics work, and (3) moral or ethical questions about when psychotropics should be used. In the rest of this chapter I will very briefly outline each of these categories of questions; the rest of the volume will then consider each of these categories and questions in turn, exploring them in more detail.

Conceptual questions raised by the effects of psychotropics

Psychopharmacology raises questions about a number of categories employed in psychiatry. Most importantly, it raises the question of how