

The creation of the concept of an antidepressant: An historical analysis

Joanna Moncrieff

Department of Mental Health Sciences, University College London, London, UK

Available online 5 March 2008

Abstract

The concept of an “antidepressant” implies a drug that acts in a disease specific way to reverse the neuropathological basis of the symptoms of depression. However, there is little scientific research that could confirm this view. This paper reports an historical study of the emergence of the concept of the antidepressant and the social forces that influenced its adoption. Historical literature documents the increasing importance of the specificity of medical treatments in the 20th century and the increased power that they conferred on medical practitioners. In the case of depression, stimulants were used as treatment from the 1940s. During the 1950s the anti-tuberculous drugs iproniazid and isoniazid started to be portrayed as more specific than stimulants, even though their stimulant effects were well documented. When imipramine was suggested to be effective in depression, it was presented solely as acting in a disease specific way and it was soon referred to as an “antidepressant”. The idea that some drugs have a specific action on the underlying basis of depression caught on rapidly and was well established by the 1960s before any evidence was available to support this view. Forces that could have driven the adoption of this view include the psychiatric profession’s desire to integrate with general medicine to improve its social status and to move away from the asylum into the community. Physical interventions and drug treatments helped to boost its medical credentials and antidepressant drugs provided a convenient form of medical treatment for community-based distress. They also helped the profession to counter attacks from the antipsychiatry movement. The pharmaceutical industry too helped to establish and disseminate the view of antidepressants as disease specific treatments in order to distinguish them from non-specific drugs. This study raises questions about the view that psychiatry was transformed into a modern medical enterprise in the 1950s and 1960s by the introduction of disease specific drugs.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Antidepressants; Depression; History of psychiatry; Pharmaceutical industry; Psychiatric profession

Introduction

Intense marketing of antidepressants over recent decades has resulted in a dramatic rise in their use, and in the widespread acceptance that depression is caused by a chemical imbalance that can be rectified by drugs. In 2002, 11% of women and over 5% of men were taking

antidepressants in the United States (Stagnitti, 2005). This situation led Nikolas Rose (2004) to conclude that a large proportion of people have come to “recode their moods and their ills in terms of their brain chemicals”. Although there has been some criticism of levels of prescribing, and recent guidelines recommend that use of antidepressants is restricted to people with more severe conditions (National Institute for Clinical Excellence, 2004), the idea that an antidepressant drug can reverse depression has not been scrutinised.

E-mail address: j.moncrieff@ucl.ac.uk

Certain drugs have been known as “antidepressants” since the 1950s. Since that time they have been thought to act as specific treatments for depression according to what can be called a “disease centred” theory of drug action (Moncrieff & Cohen, 2006). This theory or model suggests that drugs exert their effects by reversing the abnormal brain state that gives rise to symptoms, or by rectifying a biochemical imbalance. This contrasts with an earlier understanding of the action of drugs in psychiatric conditions, which can be called a “drug centred” model. This is the idea that rather than correcting abnormal brain states, psychiatric drugs induce abnormal states such as sedation or stimulation. These states may sometimes be helpful in psychiatric conditions or alternatively drug induced effects may mask the manifestations of the disorder and so create the impression of improvement.

Views about how psychiatric drugs worked changed during the 1950s. Prior to this drugs were understood as acting in a drug centred fashion, usually acting as chemical restraints. However, the new range of psychiatric drugs introduced from the 1950s onwards came to be seen as having disease specific actions. Although at first drugs like chlorpromazine, first referred to as “neuroleptics,” were believed to act through inducing an abnormal neurological state, they soon came to be seen as treating the underlying basis of psychotic symptoms and even of schizophrenia itself (The National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group, 1964; Whittaker, 2002). In line with this view they became known as “antipsychotics”. Drugs that became known as “antidepressants” were also introduced in the late 1950s.

Foucault (1973) suggests that modern disease theory started to emerge at the beginning of the 19th century when diseases came to be seen as discrete processes that could be located within particular parts of the body. This view contrasted with the older “humoral” notion of disease as a general state of bodily imbalance. However, historians Edmund Pellegrino and Charles Rosenberg suggest that it was only during the late 19th and early 20th century that the new outlook was widely accepted. The idea that substances might have specific actions on disease processes was first clearly articulated at the end of the 19th century by Paul Erlich, the discoverer of tetanus antitoxin and arsenic treatment of syphilis. He described the new drug therapies as “magic bullets” that could chemically target the infective agent without affecting the rest of the body (Mann, 1999). At first these ideas were greeted by scepticism among medical practitioners and their patients and much medical practice

continued along humeral lines. However, over the first decades of the 20th century confidence in science and scientific medicine grew. There was an acceptance of the disease theory of medicine and therapeutics among professionals and the public even before many effective medical treatments were available. Medicine became strongly associated with specialism and “cure by specific therapy” became the “only really proper sphere for the physician” (Pellegrino, 1979, P 255).

The new ideas brought with them a change in the nature and status of the medical profession and its relation to science. Prior to modern conceptions of disease and treatment, drug taking and prescribing were part of a “fundamental cultural ritual” based on the shared humeral model of bodily health and disease (Rosenberg, 1977). In this context, patients and doctors had a more equal relationship than today. People took home remedies to produce purging and frequented quacks as well as regular physicians and all treatments were based on the same principles. By contrast, modern ideas about disease and its treatment require a detailed technical understanding of the specific mechanisms of disease that is not available to the layman. Through the exclusive possession of this technical knowledge, the medical profession acquired “enormous social power” (Rosenberg, 1986, P 25). In return doctors were expected to deliver more potent therapies.

Therefore, from the late 19th century the whole of medicine was seeking disease specific treatments, a process that resulted in some very effective drugs being developed starting with antibacterials like sulphonamides and hormones including thyroxin and insulin. Thus, in developing disease specific models of treatment, psychiatry was following a general trend within medicine; one that offered the hope of more effective therapies and promised to empower medical professionals. Most research on the history of psychiatry has accepted the portrayal of modern psychiatric drugs as specific or disease centred agents. Hence drugs are often credited with revolutionising psychiatry by bringing it in line with medical science and breaking the influence of psychoanalysis and social psychiatry (Shorter, 1997).

However, elsewhere I have pointed out that there is little evidence to support the assumption that psychiatric drugs act in a specific, disease centred manner (Moncrieff & Cohen, 2005; Moncrieff & Cohen, 2006). In the case of antidepressants, recent meta-analyses suggest that their advantage over a placebo pill is small, and possibly clinically meaningless (Kirsch, Moore, Scoboria, & Nicholls, 2002; National Institute for Clinical Excellence, 2004), and it has never been demonstrated that they have consistently superior

effects to other drugs with psychoactive properties. Contrary to popular belief, it has not been demonstrated that depression is associated with an abnormality or imbalance of serotonin, or any other brain chemical, or that drugs act by reversing such a problem (Moncrieff & Cohen, 2006).

Against this background, it is interesting to look at how drugs now classed as antidepressants came to be seen as disease specific treatments for depression. In this paper, I will trace the development of the concept of the antidepressant during the 1950s and 1960s. I will also examine what extra-scientific forces may have influenced the adoption of this view of the nature of drugs used to treat depression, focusing, in particular, on the interests of the psychiatric profession and the pharmaceutical industry.

Methods and sources

A range of sources was identified for this project in order to capture attitudes to and beliefs about early antidepressant drugs. The two principle British psychiatric textbooks of the mid 20th century were identified by an eminent psychiatrist, Alec Jenner, who trained and practised during this period. One of these, *Henderson and Gillespie's Textbook of Psychiatry*, was first published in 1927 and was published in nine editions up to 1962. *Clinical Psychiatry* was published in three editions between 1954 and 1969. He also identified a well known and widely read textbook covering physical treatments in psychiatry published in 1944 (Sargant & Slater, 1944). For a previous project, I had examined all papers published in the *British Journal of Psychiatry* every 10 years from 1905 and every 5 years from 1930 to 1965. For the current research, I also examined articles published in the *American Journal of Psychiatry* in the three issues available for 1940, all issues for 1950 and all issues published in 1960.

Key early research papers on antidepressants were identified from previous historical research, and further important papers were retrieved from MEDLINE searches from 1950 to 1962 using the text word “antidepressant”. The title and identity of the authors were used to gauge the importance of papers identified in this way. I also located three specialist psychopharmacology books published between 1955 and 1967 from historical library catalogues and two sets of papers from psychopharmacology conferences held in 1959 and 1962. By virtue of working as a local doctor, I was able to obtain access to clinical case-notes of patients admitted to two London hospitals between 1940 and 1960 that were stored in the medical records department.

In order to examine extra-scientific influences on ideas about the nature of psychiatric drug treatments, I looked at publications by the psychiatric profession, especially its professional bodies such as addresses by the president of the Royal College of Psychiatrists which were published as editorials in the *British Journal of Psychiatry* and publications of the American Psychiatric Association. There is also useful secondary literature on issues concerning the profession during the mid 20th century. I looked at pharmaceutical advertisements in the *British Medical Journal* that were available from 1961 to 1965 and in the *American Journal of Psychiatry* from 1930 to 1965. These were examined for how they portrayed the nature and action of the drug they were advertising.

All reported findings were cross-checked in more than one source where possible.

Results

Treatment of depression prior to the 1950s

Although melancholia is a longstanding psychiatric diagnosis, there was little coverage of depression in textbooks or journals prior to the 1940s, apart from in the context of manic depression. It was generally felt that there was “no specific form of therapy” for depression or for mania (Henderson & Gillespie, 1927, P 154). However, patient notes demonstrate that sedative drugs were commonly prescribed to people with features that would now be classified as depression and from the 1930s amphetamines and other stimulants were also used. In other research, Nicolas Rasmussen (2006) has shown that stimulants were marketed as antidepressants from the 1940s onwards and helped to define a market for the drug treatment of neurosis with depressive features largely based on primary care. Rasmussen's research shows how stimulants were identified with a particular profile of depressive symptoms characterised by anhedonia above all, suggesting the beginnings of the idea of the specificity of action. Pharmaceutical advertisements examined for this study in the *American Journal of Psychiatry* in the 1940s and 1950s confirmed that stimulants were marketed for depressive conditions. However, there was little coverage of stimulants, or any other drugs, in the British textbooks examined or in the academic articles in both the British and American Journals of Psychiatry. In fact not a single paper covering stimulants was identified in any of the issues examined in either journal. The only discussion of stimulants was found in *An Introduction to Physical Methods of Treatment*

in *Psychiatry* in which it was suggested that they were not a specific treatment and also that they were not particularly helpful in depression (Sargant & Slater, 1944).

Convulsive therapy was introduced in the 1930s and by the 1940s electro convulsive therapy (ECT) was in widespread use in psychiatric hospitals. It was initially viewed as a treatment for schizophrenia but gradually it came to be seen as having its best effects in depression, particularly in involuntional melancholia (Mayer-Gross, Slater, & Roth, 1954). Although, there is still no agreement about how ECT induces its effects, it was generally regarded as acting to rectify the neuropathological basis of depression, according to various speculative theories (Paterson, 1963; Sadler, 1953). For involuntional melancholia it was described as a “specific and adequate means to relieve this common illness” (Moss, Thigpen, & Robinson, 1953, P 896). With the arrival of ECT depression came to be seen as a treatable condition that made up an important part of psychiatric practice. In 1944, the authors of the leading British psychiatric textbook claimed that “the immediate outlook in depressions, whether manic depressive or involuntional, has been transformed by the introduction of ‘shock’ treatment, first by the cardiazol method and now by electricity” (Henderson & Gillespie, 1944, P 261). Therefore by the 1950s, when the modern idea of an antidepressant drug first emerged, psychiatrists already believed that depression might respond to a specific physical intervention, namely ECT. There was also already a precedent for the use of drugs alone for milder cases.

From stimulants to “Psychic energisers”

The introduction of chlorpromazine transformed the way that drug treatment was regarded. Even before the disease centred theory of its action crystallised, chlorpromazine was received with great enthusiasm. It was viewed as being superior to previous drug treatments and it inspired extensive research and publicity (Moncrieff, 1999). It immediately stimulated a search for similar compounds and for possible drug treatments for depression (Lehmann & Kline, 1983).

The anti-tuberculous drugs that were used for the treatment of depression were initially regarded as stimulants and were known to produce serious psychiatric side effects similar in nature to those associated with amphetamine. Given that amphetamine was being widely used to treat psychological problems in general and psychiatric practice, the suggestion that other stimulants might be useful could be expected. In a paper

published in 1956, George Crane likened the effects of iproniazid to amphetamine and pointed out the frequent occurrence of “overactivity, insomnia, agitation and paranoid trends” (Crane, 1956, P 330). Hans Lehmann referred to it as a “drug with stimulant properties” (Lehmann, Cahn, & De Verteuil, 1958). Jean Delay described the immediate subjective effects of isoniazid as “a sensation approaching euphoric dynamism” (P 52) and he noted the occurrence of “psychomotor subexcitation”, insomnia and anxiety (Delay & Buisson, 1958).

However, within a short space of time a change in the conception of the effects of these drugs can be detected. There came to be less emphasis on the nature of the effects the drugs produced and more stress on their effects on the patient’s mental condition. In particular, efforts were made to distinguish them from stimulant drugs. Thus in a paper published in 1957, Crane divided the effects of iproniazid into “Therapeutic effects,” which were presented first, and “Toxic effects” including “Psychological side effects,” presented later. This is in contrast to the earlier paper in which an overall profile of the drugs’ effects was presented. In the second paper, the therapeutic response was described as “marked psychological improvement” with no reference to stimulant effects or hyperactivity. However, in the section on side effects it was briefly mentioned that 3 of the 20 subjects developed psychotic reactions and a further 15 had “behavioural disorders” or “overstimulation” (Crane, 1957).

1957 was also the year that the idea of the “psychic energiser” was first elucidated by American psychiatrist Nathan Kline and colleagues. The concept of a psychic energizer was designed to differentiate the anti-tuberculous drugs from other stimulants. It was suggested that iproniazid and similar drugs acted as “psychic energiser” in that they stimulated the psyche without stimulating the body. Stimulants by contrast showed a “general rather than a specific action” (Loomer, Saunders, & Kline, 1957, P 130). The authors argued that: “It has heretofore been impossible to increase psychic energy without simultaneously increasing motor, alerting and cerebral activity- with resulting undesirable side effects when a certain level is reached.” “But” they continued “it is our conviction that the present preparation, iproniazid, acts more selectively than any of the others” (Loomer et al., 1957, P 130). Kline et al. attributed the effects of psychic energisers to monoamine oxidase inhibition, which they linked to all stimulant drug activity. However, they did not explain how the difference between general stimulants and psychic ones was mediated.

Antidepressants

The other “antidepressant” drug that emerged around this time was imipramine. Unlike the tuberculostatic drugs, imipramine is not a stimulant. It is chemically similar to chlorpromazine, it has sedating properties and does not cause euphoria. Therefore, in contrast to stimulant drugs with their activating and euphoric effects, it was difficult to construct a drug centred rationale for why it might be useful in depression. In other words, it was difficult to see that any of the physiological and mental effects it induced would be particularly useful in someone who was depressed, especially as there were other sedatives available to address insomnia and agitation. Therefore, its use could only be rationalised on the basis that it exerted its effects by acting on the pathological basis of a depressive illness.

Imipramine was first used by Swiss psychiatrist Roland Kuhn, who has subsequently described how his experience with ECT had produced a “conviction that it must be possible to find a drug effective in endogenous depressions” (Lehmann & Kline, 1983, P 234). Kuhn is said to have tried imipramine first in patients with chronic schizophrenia who were withdrawn from chlorpromazine (Healy, 1997). Many of the patients became agitated and some became euphoric, which was attributed to imipramine, although in retrospect it seems possible that it was due to the sudden withdrawal of chlorpromazine. However, Kuhn took this as evidence that imipramine might be useful in depression. Kuhn’s (1957, 1958) reports of imipramine’s effects in patients with depression contained no quantitative data and consisted of personal impressions and opinions. Kuhn (1958) claimed that imipramine had “markedly anti-depressive properties” (P 459) and “potent antidepressant action” (P 464). He reported that people who had been depressed for years were suddenly cured, usually in two to three days and that patients and their relatives claimed “they had not been so well for a long time” (Kuhn, 1958, P 460). He described how a homosexual man had been transformed back to heterosexuality through treatment and another man had been cured of impotence.

Kuhn admitted that imipramine’s mode of action was uncertain, but he was at pains to deny that imipramine had euphoriant effects. Although Kuhn did not explicitly propose a mechanism of action, one can be inferred from his remarks. Kuhn said that if imipramine was discontinued “the illness breaks out again, usually with undiminished severity” (Kuhn, 1958, P 460). He also believed that imipramine could induce mania in susceptible individuals, a belief that has persisted ever

since in psychiatric folklore, despite the fact that controlled studies show no evidence that this occurs (Visser & Van Der Mast, 2005). Therefore, Kuhn’s report conveys the implicit idea that imipramine reverses the biochemical or physical substrate of depression. If the drug is stopped the abnormalities resurface and use of the drug may tip the patient into the opposite state of mania. Kuhn was also the first person to claim that imipramine’s effects were most pronounced in people with “endogenous depression”, a syndrome he described as consisting of “general retardation in thinking and action, associated with fatigue, heaviness, feeling of oppression and a melancholic or even despairing mood” (Kuhn, 1958, P 459). This claim also suggests a disease specific notion of the effects of imipramine. It implies that the drugs’ effects are not universal, but confined to people with a certain sort of neuropathology manifested in a particular behavioural syndrome.

Dissemination of the concept of an “antidepressant”

The evidence suggests that use of the term “antidepressant” quickly caught on. The Fig. 1 shows the number of papers published using the term “antidepressant” somewhere in the text between 1957 and 1965, as retrieved from a search of MEDLINE. By 1959, the term was being used routinely in over 100 papers. Many papers repeated the assertion that imipramine’s effects were strongest in endogenous depression. Often there was no reference to Kuhn’s paper or to anything else, suggesting that the association between the benefits of imipramine and endogenous type depression was regarded as established beyond doubt (Ayd, 1961a; Dally & Rohde, 1961). However subsequent reviews have not confirmed this association (Joyce & Paykel, 1989).

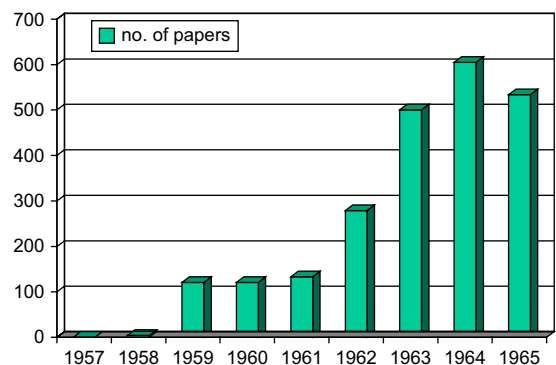


Fig. 1. Papers using term “antidepressant” on MEDLINE 1957–1965.

As early as 1959, the idea that the new drugs for depression were disease specific treatments was explicitly endorsed by prominent psychiatrists. At a conference on depression held in 1959 Professor Erik Jacobsen, referring to the anti-tuberculous drugs, expressed the belief that:

The mono-amine oxidase inhibitors seem, in theory, to be closer to the ideal psychotropic drugs, with strong and clear-cut effects on pathological states and almost no effect on normals (Jacobsen, 1964, P 210).

Jacobsen suggested that the effects of these drugs were clearly distinguishable from effects of stimulant drugs. At the same conference Pierre Deniker, a French psychiatrist who was involved in the first studies of chlorpromazine, and his colleague declared that: “The action of imipramine, and to a lesser extent iproniazid, is not merely sedative and symptomatic, like that of the neuroleptics, but is curative” (Deniker & Lemperiere, 1964, P 230).

However, some researchers questioned the view that antidepressants were disease specific drugs. Authors of an early study of imipramine noted that “similar results may have been obtained with other drugs” (Lehmann et al., 1958, P 161). Authors of a trial comparing “Drinamyl,” a widely used preparation containing barbiturates and amphetamine, with imipramine, which found no difference between the two treatments concluded “that imipramine has no specific antidepressive action” (Hare, McCance, & McCormick, 1964, P 819). Referring to tricyclic antidepressants such as imipramine, they also suggested “in so far as antidepressive drugs are effective in the treatment of depressive illness, this is in virtue of a sedative action” (Hare et al., 1964, P 819) and recommended that they should be compared with other “purely sedative” drugs (Hare et al., 1964, P 820). Authors of another study, which found no difference between the effects of imipramine and the neuroleptic thioridazine in depressed patients, concluded that they could not confirm “the specificity of action ordinarily attributed to antipsychotic and antidepressant drugs” (Overall, Hollister, Meyer, Kimbell, & Shelton, 1964, P 608).

However, these were already exceptional views by the 1960s. The overwhelming majority of research and other official information such as textbooks and formularies implicitly accepted the notion of a specific drug for depression. As early as 1960, textbooks referred to iproniazid and imipramine as “antidepressants” and distinguished them from stimulant drugs (Mayer-Gross, Slater, & Roth, 1960). Participants at a psychopharmacology conference held in 1962 also

contrasted the specificity of antidepressants to the implied non-specificity of stimulants:

The earliest reports of the use of antidepressant medication seemed to indicate that the purpose of the medication was simply some special kind of stimulation which was useful in relieving lethargy and withdrawal. It was soon evident, however, to good clinical observers, that the action of antidepressant substances was much more specific (Goldman, 1966, P 526).

The British National Formulary classification first included a category of “antidepressants” in 1963, noting that “the treatment and prognosis of mental depression has been considerably enhanced by the use of antidepressant drugs” (British Medical Association and Pharmaceutical Society of Great Britain, 1963, P 85). The old category of “stimulants” was abandoned in this edition and amphetamines and other stimulants were included in the category of antidepressants along with imipramine and iproniazid.

Antidepressants and the concept of depression

As Rasmussen (2006) has documented, by the 1950s the use of amphetamines had already carved out a niche for the use of drugs with people considered to have “neurotic depression” in general practice and for outpatients. The use of ECT had also helped to establish the idea that depression was an important and, crucially, a treatable psychiatric condition. The idea of an antidepressant strengthened the notion that depression was an important and independent category of psychiatric disorder. By 1961, leading psychiatrist Frank Ayd (1961a) characterised depression as the most common psychiatric condition. However, many psychiatrists, including Kuhn, proposed that drug treatment was only specific in cases of “endogenous depression” which was seen as equivalent to a physical disease caused by a biological disturbance. According to this view, milder conditions were seen as a reaction to life events and not thought to be particularly amenable to drug treatment. In contrast others proposed that depression was a single entity, differing only in terms of severity. The debate about whether depression was categorical or dimensional raged throughout the 1970s (Healy, 1997). However, the principle that any sort of drug treatment might be amenable to a specific type of depression helped to cement the existence of a generic category of depression. The idea of depression as a single condition won the day with the publication of DSM III in 1980, as documented by Healy (1997), which did away with the concept of neurotic or

“reactive” depression. The generic category brought together severe depressive psychosis and endogenous depression with neurotic or reactive depression and formed a rationale for the use of antidepressants in primary care and outpatient practice along clear disease centred lines. The notion of “depression” as a single and clear-cut entity also formed the basis on which the pharmaceutical industry developed an extensive market for the new antidepressants such as Prozac that emerged in 1990s. In turn, the widespread use of antidepressants helped to strengthen the concept of depression as a common biological disorder and the idea that personal problems could be attributed to a chemical imbalance. Therefore, the concept of the antidepressant helped to fashion our modern notion of depression.

Extra-scientific influences on the adoption of the idea of an “antidepressant”

The above account demonstrates that the idea of an antidepressant was embraced before there were placebo controlled trials or any evidence that might support the idea that the drugs had a disease specific action in depressive states. It is, therefore, instructive to consider what extra-scientific interests influenced the adoption of the concept of the antidepressant.

Professional interests

Professional literature demonstrates that throughout the first half of the 20th century the psychiatric profession was concerned to integrate more with general medicine to establish its scientific credentials and improve its status, along with that of its patients (Bond, 1915; Moncrieff & Crawford, 2001; Petrie, 1945). The physical treatments of the 20th century, especially ECT and insulin coma therapy, were embraced for their ability to confirm the medical nature of institutional psychiatry. Authors of a “Manual of Shock treatment in psychiatry” argued that with ECT “the psychiatrist takes on, in the patients mind, the characteristics of a ‘real doctor’ in that he is able to apply and utilise a physical method of treatment” (Jessner & Ryan, 1943, P 122). Subsequently, the new drugs introduced from the 1950s took on this role (Shepherd, 1994). In a California Senate investigation, they were credited with making “the mental hospital a medical institution in the minds of the public” and producing a “profound intensification of medical orientation” (cited in Swazey, 1974, P 209). They were also used as an argument for increasing psychiatrist numbers (Swazey, 1974).

The psychiatric profession’s other concern throughout the 20th century was to disengage itself from the

asylum. The large county mental hospitals built in the 19th century had become overcrowded with many people with chronic and severe conditions and they were perceived as a source of stigma and embarrassment for the psychiatric profession as well as their patients. By 1915, the president of the Medico-Psychological Association identified the asylum as the cause of the unpopularity of psychiatry, and recommended the establishment of “psychiatric clinics” in general hospitals. As David Armstrong (1983) has documented, medicine during the 20th century was developing a greater focus on milder conditions and their overlap with normality. Psychiatry’s increasing preoccupation with neurosis, outpatient practice, community psychiatry and the psychological health of the general population were expressions of this general trend. However, it was impossible to attract people with milder conditions to have cumbersome and dangerous procedures such as ECT and insulin coma therapy and these could not be conducted in an office-based practice. Psychoanalysis and psychotherapy were more suitable, which may partly explain their increasing popularity in this period. So was drug treatment, and drugs had the added advantage of seeming to be a proper medical treatment.

Subsequently during the 1970s, when psychiatry was under attack from antipsychiatrists and was hit by funding cuts in the United States, there was a concerted attempt to reinforce biological psychiatry and purge American psychiatry of the influence of psychoanalysis and social psychiatry (Wilson, 1993). This resulted in the publication of DSM III and the restitution of medical diagnosis to the heart of psychiatric practice and research. Drugs and their presumed specific effects formed part of the justification for this reorientation. In a response to the Rosenhan experiment, which had cast doubt on the validity of psychiatric diagnosis (Rosenhan, 1973), leading American psychiatrist Robert Spitzer, the engineer of DSM III, defended psychiatric diagnosis by referring to the specificity of treatment. He argued that evidence for the “superiority of the major tranquillisers (neuroleptics or antipsychotics) in schizophrenia, of electro convulsive therapy in psychotic depression and more recently of lithium carbonate for the treatment of mania” justified the application of a medical process of diagnosis (Spitzer, 1975, P 450).

The pharmaceutical industry

The pharmaceutical industry played a significant part in establishing the role of the new psychiatric drugs in the 1950s and beyond. In 1961, the industry was described as “launching an aggressive search for more antidepressant compounds” (Ayd, 1961a, P 32).

In the *British Medical Journal* in the first two months of 1962, eight different companies placed one or two page adverts for antidepressants, involving seven different drugs or drug combinations.

Merck, the company who finally won the patent for amitriptyline, is often credited with establishing the common use of the tricyclic antidepressants. According to David Healy, Merck distributed 50,000 copies of Frank Ayd's book, "Recognising the Depressed Patient", which suggested that depression was commoner than was generally realised and that it often went undiagnosed (Healy, 1997). Ayd suggested that one out of every 10 people required some sort of psychiatric treatment in their lifetime, most commonly for depression. He suggested that depression was most commonly encountered in general practice, where it could be treated satisfactorily by the general practitioner (Ayd, 1961b). Like more recent marketing campaigns, Merck sought to establish a concept of depression as a common *medical* condition, amenable to drug treatment.

Early antidepressant marketing reflects the opportunities that were perceived by promoting antidepressants as disease specific drugs and how this distinguished them from non-specific drugs on the market. Imipramine, marketed by Geigy as Tofranil, was described as a "specific therapeutic measure in the treatment of depression" (*Tofranil advertisement*, 1961). Nialamide (Niamid, a MAOI) was described as a "specific treatment" for "depressive illness" (*Niamid advertisement*, 1962). Phenelzine (Nardil) was claimed to be a "true antidepressant which acts selectively on the brain" (*Nardil advertisement*, 1961). A north American advertisement emphasised how it "removes the depression rather than merely masking the symptoms as do tranquillisers, CNS stimulants or sedatives" (*Nardil advertisement*, 1960). Amitriptyline was recommended for its broad profile of action, including its "intrinsic tranquillising properties" (*Tryptizol advertisement*, 1964). However, it was also described as having a "pronounced antidepressant effect" (*Saroten advertisement*, 1962a) and as being a "specific treatment for depression and anxiety" (*Saroten advertisement*, 1962b). In contrast, benzodiazepines, stimulants and occasionally neuroleptics were advertised for their non-specific drug induced effects in a range of situations, including "emotional fatigue" (*Parstellin advertisement*, 1962), "the menopause" (*Ritalin advertisement*, 1964) and the "querulousness of old age" (*Largactil advertisement*, 1964).

Discussion

Historical research involves the selection of sources and material from those sources. The sources used here

were chosen to reflect a wide range of ideas about the nature of antidepressant drugs, but ideas that were not clearly documented will inevitably be under-represented in a study based primarily on written material. Sources were predominantly British, since these were most readily available, although some American and European literature was examined. Selection is a subjective process, but validity can be improved by cross-checking material in other sources and being explicit about how sources are identified and used. The current study could not fully cover several important overlapping areas such as views about stimulant action, the evolution of the concept of depression itself and biochemical theories of depression. The monoamine theory of depression, in particular, is relevant to the way that antidepressants were portrayed as disease specific treatments but consideration of the history of this theory is beyond the scope of this paper.

This paper has charted the rapidity with which drugs that are currently regarded as "antidepressants" came to be seen as specific treatments for depressive disorders. The earliest drugs that are retrospectively regarded as antidepressants, the anti-tuberculous drugs, were clearly similar in nature to stimulants. Although stimulants had been successfully promoted as "antidepressants," by the 1950s and 1960s a distinction started to be drawn between stimulants, which were regarded as non-specific, and drugs that were thought to target depression specifically. The anti-tuberculous drugs metamorphosed into antidepressants through the concept of the psychic energizer. It was imipramine, however, that finally established the modern notion of an "antidepressant." Imipramine had to be regarded as acting on the basis of a disease, because it was difficult to see how any effects that imipramine was known to induce could be useful in depression. The idea that imipramine was an "antidepressant" caught on despite the lack of any quantitative data to support its benefits and before there were any controlled trials to establish its efficacy compared with placebo. In addition, there was and remains no evidence with which to conclude that imipramine and other antidepressant drugs act in a disease centred fashion on the biological basis of depressive symptoms.

This study challenges the conventional view of the recent history of psychiatry, which suggests that modern day drugs helped to transform psychiatry into a genuine scientific activity. This view is premised on the idea that modern drugs are disease or symptom specific treatments; that is that they work by reversing some part of an underlying physical pathology. It is this idea of the specificity of action that makes drug treatment appear as a therapeutic, medical enterprise. This

area has not been examined in previous work. David Healy's account of the history of antidepressant development charts the influence of the pharmaceutical industry and personal and professional rivalries, and it does not accept the more simplistic views of antidepressant action (Healy, 1997). Nevertheless, Healy does suggest that depression can be considered a disease and that antidepressant drugs reverse some part of a hypothetical pathological process. Therefore, it does not examine closely the nature of the first so called antidepressants and how the idea of an antidepressant emerged and was distinguished from non-specific treatments. By examining the construction of the concept of the antidepressant, the current work challenges the validity of the concept itself and raises questions about the modern notion of depression that the concept of the antidepressant helped to shape.

Like Healy's work, this study suggests that extra-scientific interests shaped our current understanding of the nature of antidepressant drugs. As such it provides an example of the way that scientific evidence can be influenced by social forces (Goldenberg, 2006). It also illustrates Rosenberg's (1977) thesis of the symbiosis between treatment specificity and professional prestige. Over the course of the 20th century there were various reasons why the psychiatric profession might wish to embrace the idea of disease specific drugs. During the early part of the century, the profession was actively seeking to improve its status through a closer association with general medicine. In addition, psychiatry was moving away from the old asylums and seeking to build up outpatient practice and community care. The antidepressants provided a medical seeming treatment for a common problem that could be treated outside hospital. The proposed specificity of drug treatments also helped the profession to weather the storms provoked by the antipsychiatry critiques and economic challenges of the 1960s and 1970s. The pharmaceutical industry helped to establish the market for antidepressants and disseminate the disease specific view of antidepressants. Therefore, this research provides an early example of the power of the pharmaceutical industry to shape scientific "facts" in the area of psychiatry (Busfield, 2006).

Over the last decade and a half, millions of people have been persuaded that their difficulties arise from a brain disorder that can be called "depression" and corrected by drug treatment. The idea of an antidepressant has been marketed to a general audience as never before. This paper challenges the validity of this concept by demonstrating that the origins of the idea lie not in robust scientific research, but instead reflect the desire of interested parties, namely the psychiatric

profession and the pharmaceutical industry, to present their interventions as specific medical therapies. The study also casts doubt on the traditional view that modern psychiatric drugs ushered in a revolution that fundamentally changed and improved the nature of psychiatric practice.

Acknowledgements

I would like to thank the Wellcome Trust for sponsoring this research and my supervisor, Virginia Berridge of the Centre for History and Public Health at the London School of Hygiene and Tropical Medicine.

References

- Armstrong, D. (1983). *Political anatomy of the body*. Cambridge: Cambridge University Press.
- Ayd, F. J., Jr. (1961a). A critique of antidepressants. *Diseases of the Nervous System*, 22(5 Pt 2), 32–36.
- Ayd, F. J., Jr. (1961b). *Recognising the depressed patient*. New York: Grune & Stratton Inc.
- Bond, C. H. (1915). The position of psychiatry and the role of the general hospitals in its improvement. *Journal of Mental Science*, 61, 1–17.
- British Medical Association and Pharmaceutical Society of Great Britain. (1963). In: *British National Formulary*. London: British Medical Association and Pharmaceutical Society of Great Britain. Alternative Edition, based on a pharmacological classification.
- Busfield, J. (2006). Pills, power, people: sociological understandings of the pharmaceutical industry. *Sociology*, 40, 297–314.
- Crane, G. E. (1956). Further studies on iproniazid phosphate; isonicotinic-isopropyl-hydrazine phosphate marsilid. *Journal of Nervous and Mental Disease*, 124, 322–331.
- Crane, G. E. (1957). Iproniazid (marsilid) phosphate, a therapeutic agent for mental disorders and debilitating diseases. *Psychiatric Research Reports*, 135, 142–152.
- Dally, P. J., & Rohde, P. (1961). Comparison of antidepressant drugs in depressive illnesses. *Lancet*, 1, 18–20.
- Delay, J., & Buisson, J. F. (1958). Psychic action of isoniazid in the treatment of depressive states. *Journal of Clinical and Experimental Psychopathology*, 19, 51–55.
- Deniker, P., & Lemperiere, T. (1964). Drug treatment of depression. In: *Depression: Proceedings of the symposium held at Cambridge 22 to 26 September 1959* (pp. 214–234). Cambridge: Cambridge University Press.
- Foucault, M. (1973). *The birth of the clinic: An archaeology of medical perception*. London: Tavistock.
- Goldenberg, M. J. (2006). On evidence and evidence-based medicine: lessons from the philosophy of science. *Social Science & Medicine*, 62, 2621–2632.
- Goldman, D. (1966). Critical contrasts in psychopharmacology. In M. Rinkel (Ed.), *Biological treatment of mental illness* (pp. 524–533). New York: L.C. Page & Co.
- Hare, E. H., McCance, C., & McCormick, W. O. (1964). Imipramine and "drinamyl" in depressive illness: a comparative trial. *British Medical Journal*, 1, 818–820.
- Healy, D. (1997). *The antidepressant era*. New York: Harvard University Press.

- Henderson, D., & Gillespie, R. D. (1927). *Henderson and Gillespie's textbook of psychiatry*. (1st ed.). Oxford: Oxford University Press.
- Henderson, D., & Gillespie, R. D. (1944). *Henderson and Gillespie's textbook of psychiatry*. (6th ed.). Oxford: Oxford University Press.
- Jacobsen, E. (1964). The theoretical basis of the chemotherapy of depression. In: *Depression: Proceedings of the symposium held at Cambridge 22 to 26 September 1959* (pp. 208–213). Cambridge: Cambridge University Press.
- Jessner, L., & Ryan, V. G. (1943). *Shock treatment in psychiatry*. London: William Heinman Ltd.
- Joyce, P. R., & Paykel, E. S. (1989). Predictors of drug response in depression. *Archives of General Psychiatry*, 46, 89–99.
- Kirsch, I., Moore, T. J., Scoboria, A., & Nicholls, S. S. (2002). The emperor's new drugs: an analysis of antidepressant medication data submitted to the US Food and Drug Administration. *Prevention and Treatment*, 5. Available from: <www.journals.apa.org/prevention/volume5/toc-jul15-02.htm>.
- Kuhn, R. (1957). Treatment of depressive states with an iminodibenzyl derivative (G 22355). *Schweizerische Medizinische Wochenschrift*, 87, 1135–1140.
- Kuhn, R. (1958). The treatment of depressive states with G 22355 (imipramine hydrochloride). *American Journal of Psychiatry*, 115, 459–464.
- Largactil advertisement. *British Medical Journal*, September 5 1964.
- Lehmann, H. E., Cahn, C. H., & De Verteuil, R. L. (1958). The treatment of depressive conditions with imipramine (G 22355). *Canadian Psychiatric Association Journal*, 3, 155–164.
- Lehmann, H. E., & Kline, N. S. (1983). Clinical discoveries with antidepressant drugs. In M. J. Parnham, & J. Bruinvels (Eds.), *Discoveries in pharmacology, Vol. 1* (pp. 209–221). London: Elsevier Science Publishers B.V.
- Loomer, H. P., Saunders, J. C., & Kline, N. S. (1957). A clinical and pharmacodynamic evaluation of iproniazid as a psychic energizer. *Psychiatric Research Reports*, 135, 129–141.
- Mann, J. (1999). *The elusive magic bullet: The search for the perfect drug*. New York: Oxford University Press.
- Mayer-Gross, W., Slater, E., & Roth, M. (1954). *Clinical psychiatry*, (1st ed.). London: Cassell & Co.
- Mayer-Gross, W., Slater, E., & Roth, M. (1960). *Clinical psychiatry*, (2nd ed.). London: Cassell & Co.
- Moncrieff, J. (1999). An investigation into the precedents of modern drug treatment in psychiatry. *History of Psychiatry*, 10, 475–490.
- Moncrieff, J., & Cohen, D. (2005). Rethinking models of psychotropic drug action. *Psychotherapy and Psychosomatics*, 74, 145–153.
- Moncrieff, J., & Cohen, D. (2006). Do antidepressants cure or create abnormal brain states? *PLoS Medicine*, 3, e240.
- Moncrieff, J., & Crawford, M. J. (2001). British psychiatry in the 20th century – observations from a psychiatric journal. *Social Science & Medicine*, 53, 349–356.
- Moss, B. F. J., Thigpen, C. H., & Robinson, W. P. (1953). Report on the use of succinyl choline dichloride (a curare-like drug) in electroconvulsive therapy. *American Journal of Psychiatry*, 109, 895–898.
- Nardil advertisement. *American Journal of Psychiatry*, XII, 1960.
- Nardil advertisement. *British Medical Journal*, January 14, 1961.
- National Institute for Clinical Excellence. (2004). *Depression: Management of depression in primary and secondary care*. [Clinical practice guideline number 23]. London: National Institute for Clinical Excellence.
- Niamid advertisement. *British Medical Journal* 1962.
- Overall, J. E., Hollister, L. E., Meyer, F., Kimbell, I., Jr., & Shelton, J. (1964). Imipramine and thioridazine in depressed and schizophrenic patients. Are there specific antidepressants drugs? *JAMA*, 189, 605–608.
- Parstellin advertisement. *British Medical Journal*, February 10, 1962.
- Paterson, A. S. (1963). *Electrical and drug treatments in psychiatry*. London: Elsevier.
- Pellegrino, E. D. (1979). The socio-cultural impact of twentieth century therapeutics. In M. J. Vogel, & C. E. Rosenberg (Eds.), *The therapeutic revolution* (pp. 245–266). Philadelphia, PA: University of Pennsylvania Press.
- Petrie, A. A. W. (1945). Psychiatric developments. The presidential address delivered at one hundred and third annual meeting of the Association on Wednesday November 29, 1944. *Journal of Mental Science*, 91, 267–280.
- Rasmussen, N. (2006). Making the first antidepressant: amphetamine in American medicine 1929–1950. *Journal of the History of Medicine and Allied Sciences*, 61, 288–323.
- Ritalin advertisement. *British Medical Journal*, October 24, 1964.
- Rose, N. (2004). Becoming neurochemical selves. In N. Stehr (Ed.), *Biotechnology, commerce and civil society* (pp. 89–128). New Brunswick, NJ: Transaction Publishers.
- Rosenberg, C. E. (1977). In: J. W. Leavitt, & R. L. Numbers (Eds.), *The therapeutic revolution: medicine, meaning and social change in 19th century America*. WI: University of Wisconsin Press.
- Rosenberg, C. E. (1986). Disease and social order in America: perceptions and expectations. *Milbank Quarterly*, 64, 34–55.
- Rosenhan, D. L. (1973). On being sane in insane places. *Science*, 179, 250–258.
- Sadler, W. S. (1953). *Practice of psychiatry*. London: Henry Kimpton.
- Sargent, W., & Slater, E. (1944). *An introduction to physical methods of treatment in psychiatry*, (1st ed.). Edinburgh: Churchill Livingstone.
- Saroten advertisement. *British Medical Journal*, January 13, 1962.
- Saroten advertisement. *British Medical Journal*, July 7, 1962.
- Shepherd, M. (1994). Neuroleptics and the psychopharmacological revolution: myth and reality. *History of Psychiatry*, 5, 89–96.
- Shorter, E. (1997). *A history of psychiatry. From the era of the asylum to the age of Prozac*. New York: John Wiley & Sons.
- Spitzer, R. L. (1975). On pseudoscience in science, logic in remission, and psychiatric diagnosis: a critique of Rosenhan's "On being sane in insane places". *Journal of Abnormal Psychology*, 84, 442–452.
- Stagnitti, M. (2005). *Antidepressant use in the US civilian non-institutionalised population, 2002*. [Statistical Brief #77]. Rockville, MD: Medical Expenditure Panel, Agency for Healthcare Research and Quality.
- Swazey, J. (1974). *Chlorpromazine in psychiatry*. Cambridge, MA: Massachusetts Institute of Technology.
- The National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group (1964). Phenothiazine treatment in acute schizophrenia. *Archives of General Psychiatry*, 10, 246–258.
- Tofranil advertisement. *British Medical Journal*, January 14, 1961.
- Tryptizol advertisement. *British Medical Journal*, September 12, 1964.
- Visser, H. M., & Van Der Mast, R. C. (2005). Bipolar disorder, antidepressants and induction of hypomania or mania. A systematic review. *World Journal of Biological Psychiatry*, 6, 231–241.
- Whitaker, R. (2002). *Mad in America*. Cambridge, MA: Perseus Publishing.
- Wilson, M. (1993). DSM-III and the transformation of American psychiatry: a history. *American Journal of Psychiatry*, 150, 399–410.