Chapter 1

A Brief History of Psychopharmacology

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1.1 Introduction

The Oxford English Dictionary defines psychopharmacology as '*the scientific study of the effect of drugs on the mind and behaviour*' (Oxford English Dictionary Online, 2018). The earliest reference to the term was in 1548 when Reinhard Lorichius published the prayer book *Psychopharmakon, hoc est Medicina Animae* (Lehmann, 1993; Wolman, 1977). Lorichius coined the term '*psychopharmakon*' to refer to spiritual medicine that could reduce human suffering. The word psychopharmacology was first used in a scientific paper in 1920 by a pharmacologist working at Johns Hopkins University who wrote a short paper entitled 'Contributions to psychopharmacology' (Macht, 1920).

The 1950s saw psychopharmacology emerge as a scientific discipline. The first textbook of psychopharmacology, *Pharmakopsycologie und Psychopathologie* by Wolfgang de Boor,

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was published in 1956 and the first journal dedicated to this research area, *Psychopharmacologia* (title subsequently changing to *Psychopharmacology*), appeared soon after in 1959. The term was first used in *Index Medicus* in 1960. *Psychopharmacology* published papers on both preclinical and clinical psychopharmacology, an approach followed by two subsequent major journals; *Journal of Psychopharmacology* and *Neuropsychopharmacology*. It was also in the 1950s that the first scientific society dedicated to psychopharmacology research was formed, the Collegium Internationale Neuro-Psychopharmacologicum (CINP), their first meeting being held in Rome in 1958 (Ban & Ray, 1996). The foundation of the American College of Neuropsychopharmacology (ACNP) followed in 1961 (Ray, 2007). The British Association for Psychopharmacology (BAP) was founded in 1974 (Green & Haddad, 2016) and the European College of Neuropsychopharmacology (ECNP) in 1985. All these societies hold regular meetings.

Many cultures have used naturally occurring psychoactive substances to alter mental functioning as part of religious ceremonies, for pleasurable effects or to alleviate mental distress. Psychedelic mushrooms and cacti were used in prehistoric times (Akers et al., 2011; El-Seedi et al., 2005). Alcohol has been fermented by many cultures for thousands of years, with the earliest documented use being in China in approximately 7000 BCE (McGovern et al., 2004). In the nineteenth century several physicians attempted to investigate the effect of naturally occurring drugs on human behaviour. They included Jacques-Joseph Moreau who studied the potential for hashish to treat mental illness (Moreau, 1845). It has only been in the last 200 years that knowledge of organic chemistry allowed scientists to synthesize non-naturally occurring drugs to alter human behaviour. A key milestone was the synthesis of barbital, the first barbiturate, in 1902 by Fischer and von Mering. The start of modern psychopharmacology is usually dated to 1949 when John Cade reported on the beneficial use of lithium in treating acute mania (Cade, 1949). This was followed by a decade of rapid drug development, the 1950s seeing the introduction of the first tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and antipsychotics, an era often referred to as the 'psychopharmacology revolution'. These developments had immense benefit for patients and their families and also spurred research into the biological causes of psychiatric illness.

Today psychopharmacology is a key part of the management of many psychiatric disorders. This does not in any way invalidate the importance of psychosocial factors in the aetiology of mental illness or of psychosocial interventions in their treatment. The optimum outcome for a person with a mental health disorder results from an individualized package of care and this will often incorporate psychopharmacological, social and psychological treatments. Furthermore, for many psychiatric disorders, especially those that are milder, the most appropriate treatment is to use psychosocial interventions alone.

The areas covered in this chapter fall into three main parts. The first part reviews the development of drugs to treat psychiatric illness from 1850 to the current time. Most attention is devoted to drug development since 1950. It is not possible, nor would it be of interest to most readers, to exhaustively review each new drug or drug class that has entered use since 1850. Rather, we have chartered some of the major developments that have occurred over this time. The middle part of the chapter reviews preclinical psychiatric drug development including the preclinical research that led to ideas about the mechanism of action of psychiatric drugs and several of the current pharmaceuticals available. The last part of the chapter examines the benefits that have stemmed from

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psychopharmacology, the controversies it has generated and the problems that the field currently faces.

1.2 Clinical Psychopharmacology 1850 to 1900

The second half of the nineteenth century saw the introduction of a range of sedative and hypnotic drugs that were widely used to treat behavioural symptoms of psychiatric disorders within the asylums. Some of these drugs were alkaloids and as a result psychopharmacology in the second half of the nineteenth century has been referred to as the '*alkaloids era*' (Shorter, 1997). However, the reality is that a wider range of drugs than alkaloids were used during this period.

Alkaloids are a group of naturally occurring nitrogenous bases. The earliest alkaloid used in psychiatry was morphine which was isolated from opium in 1805 by the German pharmacist Friedrich Sertürner. Wilhelm Griesinger (1861) highlighted the role of opium in treating various psychiatric symptoms, including anxiety and excitement, in the second edition of his textbook *Pathology and Treatment of Mental Diseases*. The alkaloids that were most widely used in psychiatry were those isolated from species of the Solanaceae family of flowering plants. This included hyoscyamine, isolated in 1839, and hyoscine (also called scopolamine), isolated in 1880. Hyoscyamine and hyoscine were often used as part of drug 'cocktails' administered in the asylums to control severe agitation. Norton (1979) refers to the 'Hyoscine Co A' cocktail, a mixture of hyoscine, morphine and atropine that was used in the 1930s to control agitation, aggression and excitement at the Bethlem Royal Hospital, London.

Chloral hydrate was synthesized in 1832. It started being used as a hypnotic in 1869 and was widely used for this indication throughout the remainder of the nineteenth century. Bromides were also widely used in the second half of the nineteenth century as sedatives and anticonvulsants. Indeed, until the introduction of phenobarbitone in 1912, potassium bromide was the only effective anticonvulsant drug (Pearce, 2002). The side-effects of bromides, plus their long half-life, meant that prolonged use could lead to their accumulation in the body. Symptoms of bromide toxicity (bromism) included neurological and psychiatric symptoms (restlessness, irritability, ataxia, confusion, hallucinations, psychosis and, in severe cases, coma), gastrointestinal effects (nausea, vomiting, anorexia, constipation) and rashes (Tillim, 1952). The bromides were replaced by the barbiturates in the early twentieth century. Much later it was discovered that all these drugs worked in one way or another on the $GABA_A$ receptor system in the brain.

The 1880s saw the introduction of paraldehyde, the cyclic trimer of acetaldehyde, into medicine. It became widely used as a sedative and anticonvulsant. Norton (1979), reflecting on his experience of working as a psychiatrist in the UK in the late 1930s, commented '*The smell of this last drug* [paraldehyde] *contributed – with that of the rubber chamber pots and the rubber lining of the padded room – to the characteristic odour of acute psychiatric wards all over Britain.*' Intramuscular paraldehyde continued to be used to treat severe agitation in psychiatric wards in the UK up to the 1980s (Holden & Cavanagh, 1987).

The nineteenth century witnessed several important discoveries by chemists in Germany that laid the foundation for the synthesis of new drugs in the twentieth century. In 1883 the structure of the phenothiazine ring was deduced by Heinrich Bernthsen, an industrialist chemist, who was trying to develop artificial dyes to replace more expensive natural dyes (Ohlow & Moosmann, 2011). The phenothiazine ring was used to synthesize

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chlorpromazine and other phenothiazine antipsychotics in the 1950s. In 1887 Lazăr Edeleano synthesized amphetamine, though its stimulant properties were not recognized until the 1930s. In 1899 Friedrich Thiele and Otto Holzinger deduced the structure of the iminodibenzyl nucleus, two benzene rings joined together by a nitrogen atom and an ethylene bridge. This structure was used by Geigy Pharmaceuticals to synthesize imipramine, the first TCA, in the 1950s.

1.3 Clinical Psychopharmacology and Physical Treatments 1900 to 1949

In 1903 two chemists at Bayer, Emil Fischer and Joseph von Mering, synthesized barbital, the first barbiturate. This was marketed as Veronal. It was followed by phenobarbital, marketed as Luminal, in 1912. By the 1950s over 2000 barbiturates had been synthesized of which approximately 50 were introduced into clinical practice as hypnotics, sedatives, anticonvulsants and general anaesthetics. The barbiturates replaced the bromides as drugs of choice as sedatives, hypnotics and anticonvulsants.

The first half of the twentieth century also saw the introduction of various new physical treatments for severe mental illness. In 1917 the Austrian psychiatrist Julius Wagner-Jauregg introduced malarial therapy for neurosyphilis, for which he was later awarded a Nobel Prize (Tsay, 2013). Malarial therapy was effective in arresting the course of neurosyphilis in some patients as the fever associated with malaria killed the bacteria *Treponema pallidum* that causes syphilis. The treatment was associated with significant mortality. Malarial therapy became obsolete in the 1940s after Stokes et al. (1944) reported the effectiveness of penicillin in treating neurosyphilis, including general paralysis of the insane (GPI). GPI was a common cause for admission to asylums in the first half of the twentieth century. Its symptoms included grandiose delusions, ataxia, asymmetrical pupils and dementia and prior to the introduction of effective treatments it was fatal. GPI virtually disappeared following the introduction of penicillin.

In the 1920s barbiturate-induced deep sleep was used to treat schizophrenia (Windholz & Witherspoon, 1993). In the 1930s, Manfred Sakel, a psychiatrist working in Vienna, introduced insulin-coma treatment, also known as insulin-shock treatment. The treatment was introduced to Britain in 1935 and became widely used, predominantly to treat schizophrenia. Insulin injections were given to induce a coma and, in some cases, a seizure. After approximately 20 minutes the coma would be reversed by administering glucose, either intravenously or via a nasal tube. Treatment was given most days for several weeks. Side effects included brain damage and it is estimated that there was a 1% mortality rate (Jones, 2000).

Another so-called 'shock treatment' was introduced in 1937 by Ladislas von Meduna, a Hungarian physician, who provoked seizures by the intravenous injection of pentylenetetrazole (also known as Metrazol and Cardiazol) primarily as a treatment for schizophrenia. The seizures were difficult to control and when severe could lead to spinal fractures. By the mid-1940s chemically induced seizures had been replaced by electroconvulsive therapy (ECT) as an electric shock was a more reliable and safer method for seizure induction (McCrae, 2006). Moreover, ECT did not suffer the adverse effect of anxiety generation that pentylenetetrazole did if a seizure was not produced and which could be profoundly distressing to the patient (Nutt, 1990).

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A surgical approach to changing brain function called prefrontal leucotomy was developed by António Egas Moniz, a Portuguese neurologist, in the 1930s and led to him being a joint recipient of the 1949 Nobel Prize in Physiology or Medicine. Moniz was previously, and unsuccessfully, nominated on two occasions for a Nobel Prize for his work on cerebral angiography. Moniz's operation entailed cutting the pathways from the frontal cortex to the rest of the brain. He conducted the first prefrontal leucotomy in 1935. The first such operation was performed in the UK in 1940 (Hutton et al., 1941) and between 1942 and 1954 it is estimated that approximately 10 000 patients in England and Wales underwent this treatment (Tooth & Newton, 1961). Side effects included brain damage, marked personality change and epilepsy, and the mortality of the procedure was approximately 3% (Board of Control for England and Wales, 1947).

Over time, insulin-coma, barbiturate-induced deep sleep treatment and leucotomy were all recognized as having no benefit and became obsolete. The demise of insulin-coma partly reflected a trial that showed no difference in outcome between patients receiving insulin-coma treatment and those who had a period of unconsciousness produced by barbiturates (Ackner et al., 1957). Although both insulin-coma and leucotomy were on the wane by the early 1950s, the introduction of the first antipsychotic drugs in the mid-1950s contributed to their demise. The use of ineffective physical treatments during the first half of the twentieth century partly reflects the fact that at that time evidence-based medicine did not exist. In addition, the suffering caused to patients and their families by mental illness, the absence of any effective treatment and the poor conditions within asylums (overcrowding, underfunding and understaffing were commonplace) meant that clinicians were desperate for new therapies that offered hope. The only physical treatment introduced in that period that remains in use today is ECT. Today, ECT is largely used as a treatment option for severe depressive illness in urgent or emergency situations, such as depressive stupor, or where other treatments have failed (Cleare et al., 2015). There is a strong evidence base supporting the efficacy of ECT in severe depression (see Chapter 16). Current practice for ECT involves the patient being given a general anaesthetic and administered a muscle relaxant to attenuate the muscular activity in the seizure. This is in contrast to the use of unmodified ECT in the 1940s, when the electroshock was given without anaesthesia and a muscle relaxant, and the treatment was used in a much broader range of disorders, including schizophrenia.

In 1937 Charles Bradley, a psychiatrist working in Rhode Island, reported a small study that showed that Benzedrine (amphetamine sulphate) led to a marked improvement in the behaviour and school work of children with behavioural problems (Bradley, 1937). This was the first report that psychostimulants could treat certain behavioural problems in children. Bradley confirmed his findings with a second larger study published in 1940 (Bradley & Bowen, 1940). His work received little attention for the next 20 years and it has been suggested that this reflected the prevailing view that behavioural problems did not have an underlying biological cause and that psychological interventions alone were required (Lange et al., 2010). In the mid-1950s another stimulant drug, methylphenidate, started being used as a treatment for children with what would now be diagnosed as attention deficit hyperactivity disorder (ADHD). At that time methylphenidate was also used for various indications in adults including the treatment of chronic fatigue, depression and narcolepsy (Physicians' Desk Reference, 1956).

The first half of the twentieth century saw a variety of drugs being used to treat depression including amphetamine and tincture of morphine and various vitamins and

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hormones but none was successful. So, in summary, advances in drug treatments for psychiatric disorders in the first half of the twentieth century were limited. The major successes were penicillin as a treatment for neurosyphilis and the introduction of barbiturates to treat anxiety and sleep disturbance, though barbiturates were often fatal in overdose. A series of physical treatments were also introduced that were later shown to be ineffective, the exception being ECT, which remains an important treatment option primarily for severe depression. There were no effective drugs to treat depression or schizophrenia, but this situation changed dramatically in the 1950s.

1.4 The 1950s and the Psychopharmacology Revolution

The 1950s saw the introduction of the first antidepressant and antipsychotic drugs, the early development of randomized, placebo-controlled clinical trials to assess drug efficacy and the creation of psychopharmacology as a discipline. The importance of this decade is highlighted by the fact that it is often referred to as the 'psychopharmacology revolution'. The first breakthrough came in 1949 when the Australian physician John Cade reported the benefit of lithium in treating manic patients with 'psychotic excitement' (Cade, 1949). Lithium had been used in the nineteenth century to treat gout and mood disorders but Cade's paper triggered renewed interest in lithium. In Denmark Mogens Schou and colleagues conducted the first randomized placebo-controlled trial of lithium demonstrating its efficacy in acute mania (Schou et al., 1954). In the late 1960s and early 1970s a series of trials showed the efficacy of lithium in the maintenance phase of bipolar illness (Angst et al., 1970; Baastrup & Schou, 1967; Baastrup et al., 1970). Current clinical guidelines for the management of bipolar disorder, from the National Institute for Health and Care Excellence (NICE, 2014) and the British Association for Psychopharmacology (Goodwin et al., 2016), regard lithium as the first-line option for maintenance treatment (see Chapter 11).

The world's first antipsychotic drug was chlorpromazine, a phenothiazine. It was synthesized in 1950 by Paul Charpentier, a chemist working for the French pharmaceutical company Rhône-Poulenc. It was developed as part of the company's antihistamine development programme. In keeping with contemporary practice, the company gave samples to interested clinicians so that they could report on its clinical effects. The French naval surgeon Henri Laborit noted that when it was used as a pre-anaesthetic agent it produced calming without excessive sedation and suggested its possible use in psychiatry. In 1952 Jean Delay and Pierre Deniker (Figure 1.1), working at St Anne's Hospital in Paris, reported on chlorpromazine's beneficial effects in treating psychotic patients with disturbed behaviour (Delay et al., 1952). Originally it was thought that chlorpromazine worked by inducing 'artificial hibernation' and so ice packs were used at St Anne's Hospital to enhance its effects, but it quickly became apparent that therapeutic effects were due to the drug alone (Thuillier, 1999). At the same time as Delay and Deniker's work, several other psychiatrists published case reports that supported the efficacy of chlorpromazine (e.g. Hamon et al., 1952).

Delay and Deniker organized an international colloquium on the psychiatric uses of chlorpromazine in Paris in 1955 that was attended by 257 participants from 19 countries. Clinicians were impressed by the drug's benefits and felt that a new era of treatment was starting (Swazey, 1974). Chlorpromazine was quickly adopted as a treatment by psychiatrists working throughout Europe and North America. At the same time chlorpromazine

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Figure 1.1 Jean Delay (left) and Pierre Deniker (right).

was also being promoted for various non-psychiatric indications including as an antiemetic. The success of chlorpromazine in the large state psychiatric hospitals in the United States (US) partly reflected an extensive marketing campaign by Smith Kline & French who owned the US licence (Swazey, 1974) (Figure 1.2). In the UK, chlorpromazine was marketed as Largactil and in North America as Thorazine. In 1957 the American Public Health Association presented a Lasker Award jointly to Henri Laborit, Pierre Deniker and Heinz Lehmann to recognize their work in introducing chlorpromazine as a treatment for schizophrenia. The term antipsychotic was not used in the 1950s; instead chlorpromazine and related drugs were referred to as 'neuroleptics', 'ataraxic drugs' or 'tranquillisers'. Following the introduction of the benzodiazepines in the 1960s, antipsychotics started being referred to as 'major tranquillisers' to differentiate them from the benzodiazepines which were termed 'minor tranquillisers'. The term antipsychotic appears to have first been used in print by Himwich (1958).

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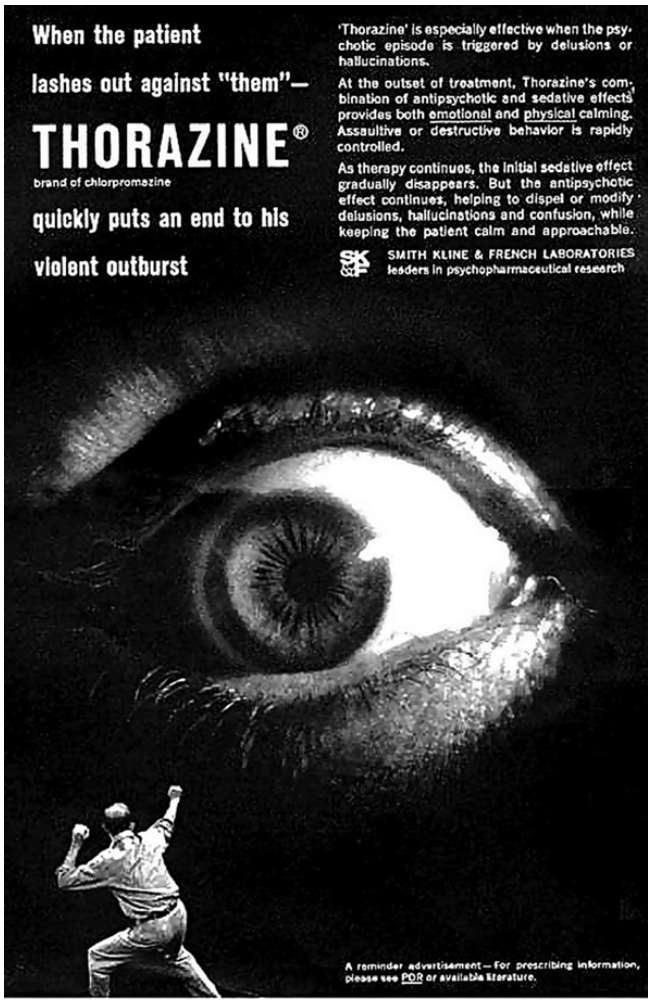

Figure 1.2 Advert for Thorazine (chlorpromazine) from the early 1960s.

The commercial success of chlorpromazine led other companies to develop other phenothiazine antipsychotics, and also, most notably, the butyrophenone compound haloperidol, synthesized in 1958 by Janssen Pharmaceutica.

The development of phenothiazine-related compounds by Geigy resulted in a further unexpected development. The clinical evaluation of imipramine, a drug structurally similar to chlorpromazine (Figure 1.3), failed to detect any noticeable antipsychotic effect, but the psychiatrist Roland Kuhn, working in Munsterlingen, Switzerland, reported that it had antidepressant effects (Brown & Rosdolsky, 2015; Kuhn, 1958). This observation was pivotal in Geigy introducing imipramine as a treatment for depression in Europe in 1958 and in the USA the following year. It was the first TCA and led to other companies developing and marketing TCAs and closely related compounds. By the early 1970s randomized placebo-

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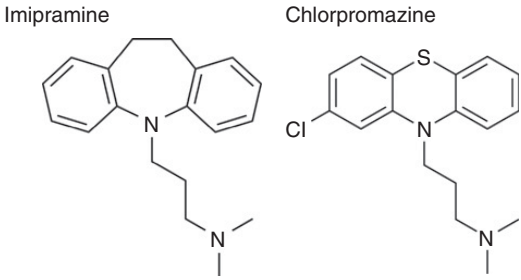

Figure 1.3 Chemical structures of imipramine and chlorpromazine.

controlled trials had demonstrated the benefit of maintenance treatment with TCAs in reducing the risk of relapse of depression (Mindham et al., 1972).

In 1957 Nathan Kline, working in New York, reported that iproniazid, an anti-tuberculous drug, had antidepressant effects (Loomer et al., 1957). Iproniazid was the first MAOI and was followed by others including phenelzine (Figure 1.4), isocarboxazid and tranylcypromine. In the 1960s, the MAOIs fell out of favour partly due to concerns about both hepatotoxicity and their interactions with foodstuffs and other medications (Blackwell, 1963). A Medical Research Council-sponsored trial also cast doubts on their efficacy, though this may have partly reflected under-dosing of phenelzine, the MAOI used in the study (Medical Research Council, 1965). Today, the use of MAOIs is restricted to treatment-resistant depression, with prescribing tending to be limited to clinicians experienced in their use and who often work in tertiary affective disorder centres. Anecdotally it seems that some patients with depression respond to MAOIs when they have failed to respond to other antidepressants and it has been argued that MAOIs are currently underused by psychiatrists.

Although the first trials of antidepressants, antipsychotics and lithium focused in demonstrating their acute efficacy, subsequent randomized controlled trials (RCTs) showed that continued treatment with each of these drugs reduced the risk of relapse in people who had initially responded to acute treatment with that medication. This meant that for the first time it was possible to prevent the recurrence of major psychiatric illness. Furthermore, this benefit applied to people with depression, schizophrenia and bipolar disorder.

The year 1955 saw the launch of meprobamate for the management of anxiety though it was also promoted to treat other psychiatric disorders including psychosis (Green et al., 2018a). Its trade name was Miltown, named after Milltown, a village near the Wallace laboratories in New Brunswick, USA, where it was synthesized. It was the first 'blockbuster' drug in psychiatry and initially promoted as a safer anxiolytic than the barbiturates which were dangerous in overdose. However, by the 1960s the addictive potential of meprobamate was recognized and by 1970 it was listed as a controlled drug in the USA. In 2012 the European Medicines Agency withdrew the marketing authorization in the European Union for all medicines containing meprobamate due to concerns about adverse effects including addiction (European Medicines Agency, 2012). A recurrent theme in the history of anxiolytic drugs is delayed recognition of the potential of a new drug to be associated with dependence and also recreational misuse; this was first seen with the barbiturates and later repeated with meprobamate, the benzodiazepines and most recently pregabalin (Schjerning et al., 2016).

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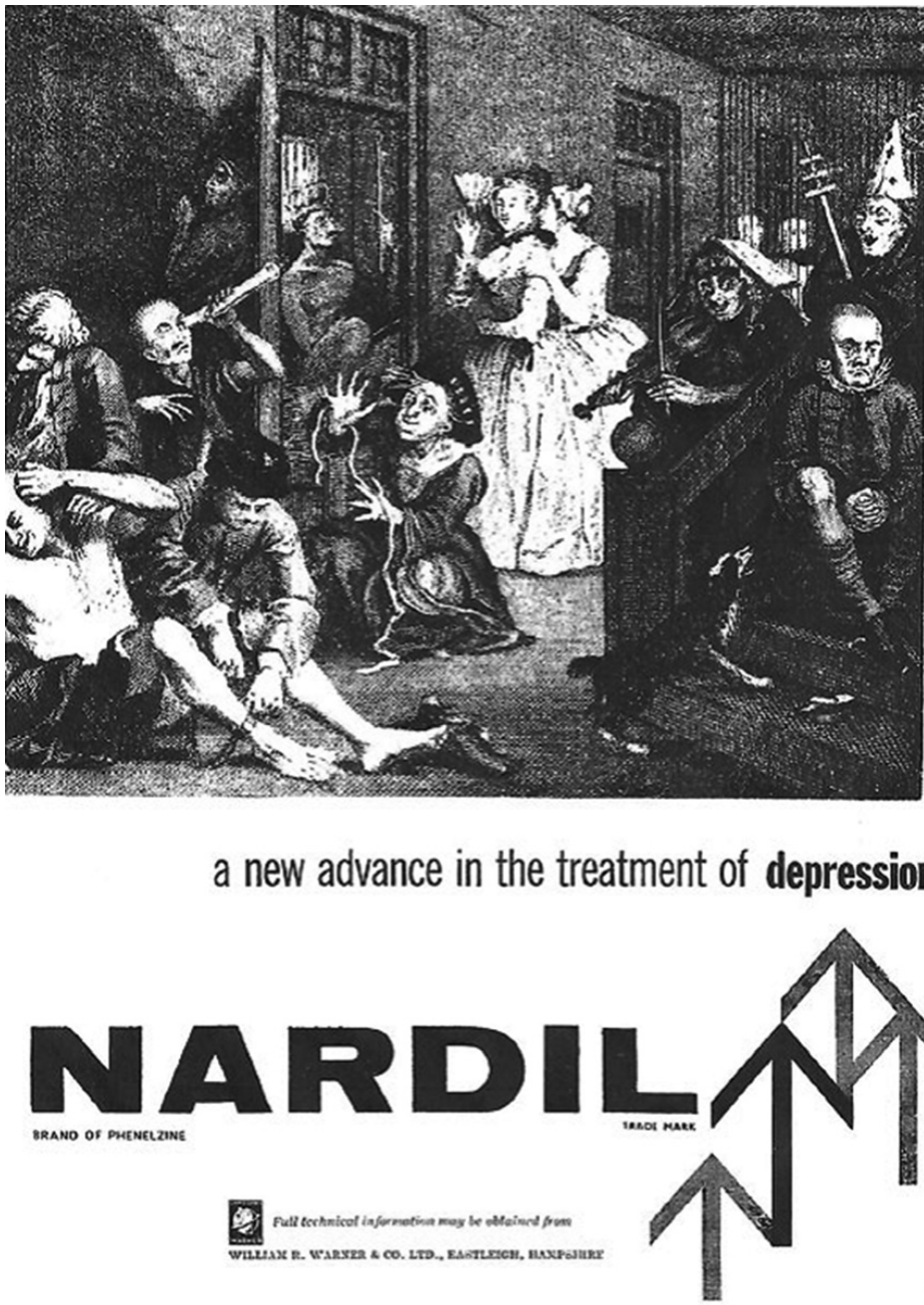

Figure 1.4 Advert for Nardil (phenelzine) from *British Medical Journal* (1960).

The introduction of chlorpromazine, imipramine and iproniazid into psychiatric practice each resulted from clinicians observing a benefit of the drug in patients with conditions different to those the manufacturer had originally proposed. All three drugs

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entered clinical practice without any supporting placebo-controlled RCTs, reflecting the much less rigorous process for drug development and approval in the 1950s compared with today. One often reads that these drug discoveries were 'serendipitous' but this is oversimplistic. Each reflected far more than chance or accident; there was a rationale as to why the company developed the drug and why it was first used in psychiatric patients. Astute clinical observations, not chance, led to a benefit being observed. In addition, the very basic understanding of pharmacology in the 1950s and 1960s meant that the 'discovery' of many drugs at that time, in all branches of medicine, followed a similar path. It was only decades later that technology and pharmacological knowledge were sufficient to design drugs in the laboratory to act on specific receptors and other pharmacological targets (see Chapter 2). With regard to the discovery of the psychiatric benefits of chlorpromazine, Rhône-Poulenc had been developing sedative antihistamines for many years. They had reason to suspect that a more centrally acting compound could have clinical applications as a pre-anaesthetic agent, partly based on clinical reports from Laborit regarding their earlier drug promethazine. As a result, the more lipophilic analogue chlorpromazine was synthesized. As already described, Laborit observed that it caused calming without sedation and this led to several psychiatrists using it in patients with marked behavioural disturbance. The detailed reports of Delay and Deniker and their contemporaries confirmed the drug's benefits in the treatment of patients with mania and schizophrenia. As Sir John Gaddum, the father of monoamine neurotransmitter research in the UK, commented '*It is true that many discoveries* [in pharmacology] *have been accidents, but these accidents would not have occurred to anyone who was not engaged in a systematic research for new knowledge, and without the techniques and apparatus of modern science they would usually have passed unheeded in the modern world*' (Gaddum, 1954).

Finally, it is notable that recent investigations, using advertising in the *British Medical Journal* during the 1950–80 period as an index of the rise of modern pharmaceuticals in several major therapeutic areas (cardiovascular, respiratory, gastrointestinal and central nervous system (CNS) diseases), observed that one of the first areas to benefit from the launch of novel effective medications was psychiatry (Green et al., 2018a, 2018b). A significant number of these drugs, or their related descendants, are still widely used today.

1.5 Clinical Psychopharmacology 1960 to 1979

The 1960s saw the results of the first large, double-blind, placebo-controlled RCTs in psychiatry. Of particular note was a series of RCTs that supported the efficacy of antipsychotic drugs in schizophrenia. These included two RCTs conducted in Veterans Administration (VA) centres that demonstrated that phenothiazines were superior to placebo in treating overall symptoms in chronic inpatients (Adelson & Epstein, 1962; Casey et al., 1960). More impressive still were the data in one of those studies relating to the proportion of patients deemed well enough for discharge when the study ended and blinding was broken; 36% in the antipsychotic-treated group versus 5% in the placebo-treated group (Adelson & Epstein, 1962). A weakness of both VA studies was that the participants were all long-term inpatients. This was overcome when a third trial, conducted by the National Institute of Mental Health (NIMH), was published in 1964 showing the superiority of antipsychotics compared with placebo in acute inpatients with

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schizophrenia (National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group, 1964). This study also showed that the benefit of antipsychotics extended beyond treating overactivity and behavioural disturbances, i.e. antipsychotics were shown to be effective in treating a wide range of symptoms of schizophrenia including auditory hallucinations, ideas of persecution, hebephrenic symptoms and incoherent speech, as well as irritability and hostility.

Soon after the antipsychotics were introduced it became apparent that many patients with schizophrenia who were discharged from the asylums stopped their oral antipsychotics and subsequently relapsed. To try and improve adherence, and reduce the risk of relapse, long-acting intramuscular injections of antipsychotics were developed. These were originally referred to as depots though the term long-acting injectable (LAI) antipsychotic is often used today. Fluphenazine enanthate, the first LAI antipsychotic, was introduced in 1966 (Johnson, 2009), and other LAIs followed. Whether LAIs reduce relapse rates compared to oral antipsychotics remains a subject of contention, with the most recent meta-analysis of RCTs (Kishimoto et al., 2014) showing no difference in relapse between those randomized to oral antipsychotic versus those randomized to LAIs, but with observational studies, including mirror-image studies (Kishimoto et al., 2013b) and cohort studies (Kishimoto et al., 2018), usually showing superiority for LAIs. These conflicting results seem to partly reflect trial methodology. Irrespective of their comparative effectiveness, the main advantage of LAI antipsychotics over oral antipsychotics is that LAIs make adherence transparent. Although some patients find a LAI more convenient than taking an oral antipsychotic, others do not like to receive their medication this way for various reasons, including a loss of autonomy.

The first benzodiazepine, chlordiazepoxide, was introduced in 1960 by Hoffmann–La Roche (now Roche) to treat anxiety. Diazepam was launched in 1963 and was followed by many other benzodiazepines. Some benzodiazepines with a shorter half-life, such as temazepam, were promoted as hypnotics. The benzodiazepines have a wide range of actions, including sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant. They also have amnesic properties. Their main advantage in comparison with the earlier barbiturates was that they were much less dangerous in overdose. However, the benzodiazepines, like the barbiturates, can cause tolerance and dependence and are associated with misuse, although the extent of these problems was not initially recognized by the medical profession, leading to a serious problem with iatrogenic benzodiazepine dependence. This problem was compounded by over-marketing and overprescribing. For example, a 1963 advert for Valium stated that it was for '*prisoners of the society of stress*' with the illustration showing a woman shopping. Diazepam sales peaked in the United States in the mid-1970s and since then levels of benzodiazepine prescribing have fallen. Nevertheless, a large proportion of benzodiazepine prescribing continues to be off-label. That is, it is either for disorders not specified in the drug's marketing authorization or at doses and for durations that exceed those that are approved (Lader, 2014). The overprescribing of benzodiazepines and the delayed recognition of benzodiazepine dependence remain salutary lessons for psychiatry and psychopharmacology today.

1.6 Clinical Psychopharmacology 1980 to 1999

The 1980s saw the introduction of a new antidepressant class, the selective serotonin reuptake inhibitors (SSRIs). The SSRIs were the first class of psychiatric drugs that were

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designed to act on a selective pharmacological target, in this case the serotonin reuptake transporter. As the SSRIs had little action at other pharmacological sites, they were associated with fewer side effects than the earlier TCAs which had anticholinergic, antihistaminergic and α_1-adrenoceptor-blocking actions. The first SSRI to be introduced was zimeldine in 1982. It was manufactured by Astra and withdrawn soon after its launch due to an association with Guillain–Barré syndrome (Fagius et al., 1985). The next two SSRIs to be approved were fluvoxamine, licensed in Europe in 1983, and fluoxetine, licensed in the USA in 1987. Other SSRIs followed including paroxetine, sertraline, citalopram and escitalopram.

The improved tolerability of the SSRIs meant that they could be started at a therapeutic dose, a major advantage compared with the TCAs, which had to be started at a subtherapeutic dose with the dose subsequently being gradually stepped up to allow the patient to develop tolerance to side effects such as sedation and dry mouth. The SSRIs were also much less toxic than the TCAs in overdose. Although the efficacy of the SSRIs in depression is similar to that of the TCAs, their advantages in terms of fewer side-effects, safety in overdose and ease of use meant that they were a major advance in the treatment of depression. The quality and number of RCTs that accompanied the SSRIs was superior to that for the TCAs. RCTs subsequently demonstrated the efficacy of specific SSRIs in treating a range of anxiety disorders, including obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder and post-traumatic stress disorder. The SSRIs remain first-line options today for the treatment of, and prevention of recurrence in, moderate and severe major depressive disorder. They also have an important role in the treatment of more severe anxiety disorders. Psychological interventions are generally the treatment of choice for mild depressive disorders and less severe anxiety disorders.

In 1988 a trial by John Kane and colleagues showed that clozapine was more effective than chlorpromazine in treatment-resistant schizophrenia (Kane et al., 1988). Clozapine was originally synthesized by the Swiss pharmaceutical company Wander in the 1950s but was not introduced as an antipsychotic until 1972 when it was launched in several European countries. This delay has been attributed to its lack of extrapyramidal side-effects (EPSE) leading some to doubt it was an effective antipsychotic. During the 1950s there was a commonly held view that EPSE and antipsychotic efficacy were closely linked, a view that was only disproved when the NIMH antipsychotic study was published in 1964 (National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group, 1964). The delay in the initial launch of clozapine is also likely to have reflected concerns about its propensity to cause postural hypotension and grand mal seizures. Clozapine was voluntarily withdrawn by Sandoz in 1975 after a series of cases of agranulocytosis were reported in Finland (Idanpaan-Heikkila et al., 1975). The 1988 trial of Kane and colleagues, and subsequent confirmatory studies, resulted in clozapine being licensed in 1989 by the Food and Drug Administration (FDA) for the treatment of treatment-resistant schizophrenia, with close haematological monitoring being a mandatory condition for its use. Clozapine remains the only drug licensed for treatment-resistant schizophrenia. Its superiority in this condition has been demonstrated by meta-analysis (Siskind et al., 2016) and in two large trials that recruited patients from a range of clinical settings, Phase II of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Lieberman et al., 2005) and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (Jones et al., 2006; Lewis

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et al., 2006). In the UK, NICE (2014) recommends that clozapine is offered to patients with schizophrenia who have not responded sufficiently to the sequential use of at least two different antipsychotic drugs prescribed at adequate doses, at least one of which should be a non-clozapine second-generation antipsychotic.

In 2002 the FDA approved clozapine for the treatment of recurrent suicidal behaviour in schizophrenia and schizoaffective disorder; it is not approved for this indication in Europe. The US approval for suicidal behaviour reflected the results of the International Suicide Prevention Trial (Inter SePT), a multi-centre trial that randomized nearly 1000 people with schizophrenia or schizoaffective disorder, who were judged at high risk of suicide, to treatment with either clozapine or olanzapine (Meltzer et al., 2003). During the two-year follow-up period, the proportion of people who attempted suicide was significantly lower among those treated with clozapine. Chapter 10 provides a detailed review of the pharmacology and clinical uses of clozapine.

In 1994 risperidone was approved by the FDA and became the first of the so-called second-generation antipsychotics (SGAs). Other SGAs followed, including olanzapine (FDA approval for schizophrenia, 1996) and quetiapine (FDA approval for schizophrenia, 1997), and most recently lurasidone (FDA approval for schizophrenia, 2014). The SGAs were originally thought to offer superior efficacy to the first-generation antipsychotics (FGAs), especially in the treatment of negative symptoms, and to have a reduced risk of causing EPSE. Research in the 2000s, most notably the CATIE (Lieberman et al., 2005) and CUtLASS (Jones et al., 2006; Lewis et al., 2006) studies, showed no efficacy advantage for the SGAs over the FGAs in acute schizophrenia and that the situation regarding side effects was more complex, with comparisons needing to be made at the level of individual drugs rather than comparing broad pseudo-classes such as FGAs and SGAs. Some of the second-generation drugs, especially olanzapine, carry a high relative risk of weight gain and metabolic abnormalities (i.e. elevation of plasma glucose and lipids) that was not recognized when they were initially approved. These events highlight the importance of clinicians being sceptical of marketing claims made for new products, especially before there is sufficient post-marketing surveillance, including Phase IV studies, and independent clinical trials. Now rather than calling them SGAs the preferred pharmacology term in Neuroscience-based Nomenclature (NbN) is dopamine/serotonin blockers (see Editor's Note on Nomenclature).

In 1993 tacrine, a centrally acting acetylcholinesterase inhibitor, became the first drug to be licensed for the symptomatic treatment of Alzheimer's disease (Crismon, 1994). It was withdrawn from the US market in 2012 due to concern about hepatic adverse effects. Subsequently, several other acetylcholinesterase inhibitors were approved for the symptomatic treatment of mild to moderate Alzheimer's disease including donepezil (approved 1996), rivastigmine (approved 2000) and galantamine (approved 2000). Rivastigmine was subsequently approved for the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

1.7 Psychopharmacology in the New Millennium

Two landmark studies in schizophrenia that were published in the first decade of the new millennium were the CATIE study (Lieberman et al., 2005), conducted in the United States, and the CUtLASS study (Jones et al., 2006; Lewis et al., 2006), conducted in the UK. Both studies found that there was little difference in efficacy between FGAs and SGAs in the treatment of acute schizophrenia, the exception being clozapine, which was

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superior in treatment-resistant schizophrenia. Both studies also found that there was little difference in the risk of EPSE between the specific first- and second-generation drugs that were studied. The results of CATIE and CUtLASS surprised many clinicians who had assumed that the SGAs were superior in efficacy, and had a lower EPSE risk, compared to the FGAs. The assumption that SGAs had a lower propensity than FGAs to cause EPSE probably stems from most SGA registration studies adopting haloperidol as the FGA comparator. Haloperidol has a high relative risk of EPSE while many other FGAs, such as chlorpromazine and perphenazine, have a lower risk (Leucht et al., 2013). In summary, the high risk of EPSE seen with haloperidol in many RCTs seems to have been incorrectly extrapolated to FGAs in general. Although antipsychotics differ little in terms of acute efficacy (the exception being clozapine, which is more effective in treatment-resistant schizophrenia), they differ significantly in their propensity to cause EPSE and a wide range of other side effects including weight gain, sedation, prolactin elevation, metabolic dysregulation and QTc prolongation. The differential risks of a range of antipsychotic adverse effects in people with schizophrenia have been quantified by meta-analysis (Leucht et al., 2013).

The introduction of the SGAs did have some advantages. In particular, the quality of the supporting RCTs was far superior to that of the FGA studies, some of which had been conducted more than three decades earlier. Meta-analysis showed a small advantage for SGAs versus the FGAs in the maintenance treatment of schizophrenia, the risk of relapse being slightly lower for SGAs (Kishimoto et al., 2013a). In addition, several SGAs were shown to be effective in disorders other than schizophrenia. For example, RCTs showed that several SGAs were effective in augmenting antidepressants in the treatment of major depressive disorder (Nelson & Papakostas, 2009). One SGA, quetiapine, was shown in placebo-controlled RCTs to be effective in the acute treatment of bipolar depression (Suttajit et al., 2014) and in a further RCT to reduce the risk of relapse of bipolar depression (Weisler et al., 2011). Although all antipsychotics are effective in treating acute mania and reducing the risk of manic relapse, the efficacy of quetiapine in the acute and maintenance treatment of bipolar depression is not a class effect shared by other antipsychotics. An added advantage of the quetiapine bipolar maintenance study was the inclusion of a lithium comparator arm, in addition to the quetiapine and placebo arms (Weisler et al., 2011). As such, this study, designed primarily to investigate the long-term efficacy of quetiapine, was also the largest placebo-controlled trial of lithium maintenance treatment in bipolar disorder ever conducted. It showed that lithium was superior to placebo in reducing the risk of relapse of bipolar depression as well as of mania. Previously it had been thought that lithium's benefits in the long-term treatment of bipolar disorder were largely restricted to reducing the risk of recurrence of mania rather than depression.

In 2002 the NMDA (*N*-methyl-D-aspartate) receptor antagonist memantine received European marketing approval for use in moderate to severe Alzheimer's disease, thereby becoming the first drug other than an acetylcholinesterase inhibitor to reach the market for this indication.

In 2002 the FDA approved aripiprazole for the treatment of schizophrenia. Subsequently, it received FDA approval in the USA for the treatment of bipolar I disorder (mania and mixed episodes and as a maintenance treatment) (2004), the treatment of irritability associated with autistic disorder (2009), the treatment of Tourette's disorder (2014) and as an adjunctive treatment for major depressive disorder (2006). In the UK

aripiprazole is only licensed for the treatment of schizophrenia and the treatment of manic episodes and the prevention of a new manic episode in bipolar I disorder. Aripiprazole was the first antipsychotic drug to be marketed that was a D_2 partial agonist; all previous antipsychotics are full D_2 antagonists. Subsequently, two other D_2 partial agonists, brexpiprazole and cariprazine, received FDA approval. Brexpiprazole was approved for the treatment of schizophrenia and adjunctive treatment of major depressive disorder and cariprazine for the treatment of schizophrenia and the acute treatment of manic or mixed episodes in bipolar I disorder. The three currently available dopamine partial agonists differ not only in their indications but also in the formulations, pharmacodynamics, pharmacokinetics and side-effect profiles (Frankel & Schwartz, 2017). Overall, the dopamine partial agonists have a relatively low risk of causing prolactin elevation, metabolic side effects and EPSE other than akathisia.

In 2019 eskatamine, an intranasal formulation of ketamine, an NMDA receptor antagonist, received FDA approval for use in combination with a newly commenced antidepressant in adults with treatment-resistant depression. This represents a treatment for depression that is not reliant on modulating the monoamine system and benefit can occur within hours of administering the first dose, representing a far quicker onset of action than with traditional antidepressant drugs. The FDA approval reflected positive results from short- and long-term clinical trials (Janssen, 2019). Ketamine has a number of potential drawbacks including that its effects seem transient. Its place in clinical practice is yet to be determined.

At the time of writing, a large range of psychiatric drugs are under development. For example, a recent review identified 112 agents in the current pipeline for the treatment of Alzheimer's disease (Cummings et al., 2018). Much research is also focused on the treatment of depression (Garay et al., 2017) and schizophrenia (Garay et al., 2016). One area of development in treatment-resistant depression relates to drugs that modulate the opiate system. Recent RCTs of opiate-modulating drugs in depression have produced somewhat inconsistent results (Fava et al., 2016; Zajecka et al., 2019) but overall the field remains promising and further work is warranted. Another area of interest relates to the use of psilocybin and lysergic acid diethylamide (LSD) to treat addiction, anxiety disorders and treatment-resistant depression (Dos Santos, 2018). The work on psychedelics is largely based on small open studies of a short duration (e.g. Carhart-Harris et al., 2016) but a large Phase IIb dose-ranging study of psilocybin in treatment-resistant depression is currently underway in Europe and North America (ClinicalTrials.gov Identifier: NCT03775200). Psychedelics appear only to need one or two doses to be effective and there is the suggestion that they allow brain networks to be reset (Carhart-Harris & Nutt, 2017). Caution is needed when considering any drugs in the pipeline as the failure rate in drug development in all branches of medicine is high (see Chapter 2).

1.8 Preclinical Psychiatric Drug Development 1950 Onwards

1.8.1 Introduction

It is apparent to anyone reading the earlier sections on clinical psychopharmacology and drug development in the 1950–60 era that the first drugs that became available for the treatment of both depressive illness and schizophrenia during that period (and indeed

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well beyond) did not emanate from a rational drug discovery process. Indeed, neither chlorpromazine nor imipramine were developed for these respective indications. However, their appearance on the market and evidence for their efficacy came concomitantly with the realization that certain neurotransmitters in the brain might play a role in mood disorders. Consequently, during the 1960s there was a flood of investigations on the ways that psychiatric drugs altered neurotransmitter concentrations and function in the brain of experimental animals. This discovery process was assisted by the increasingly accurate and rapid methods, primarily spectrofluorimetry, for measuring monoamines in cerebral tissue. Such studies both enhanced our understanding of the possible mechanisms by which the drugs might be producing their therapeutic effect but also, to some extent, resulted in the proliferation of drugs with the same probable mechanism of action, the so-called 'me too' drugs, as will be discussed later.

The suggestion that psychoactive drugs might be achieving their therapeutic effect through an action on brain neurotransmitters was enunciated in the early years of the 1950s. The structural characterization of the vasoconstrictive substance 5-hydroxytryptamine (5-HT; serotonin) was published in 1948 by Maurice Rapport in the USA (Rapport et al., 1948), and only four years later it was reported that this compound was present in mammalian brain by both John Gaddum in Edinburgh and Irvine Page in Cleveland, Ohio. Gaddum noted that the action of 5-HT on peripheral tissue preparations was antagonized by LSD, and in a seminal publication he suggested that since LSD produced mood change it was reasonable to speculate that cerebral 5-HT was involved in controlling mood (Amin et al., 1954). The same conclusion was reached independently in the USA by Woolley and Shaw (1954) who had observed the structural similarity between the 5-HT and LSD molecule (Figure 1.5).

The other two major monoamine neurotransmitters now known to be closely associated with the actions of psychoactive drugs were also identified in the brain in the 1950s. Marthe Vogt in Edinburgh, both identified and mapped noradrenaline (norepinephrine) in the mammalian brain (Vogt, 1954), while dopamine, a known precursor of noradrenaline, was reported in 1957 to be acting as a neurotransmitter in the brain in its own right by groups working independently in Sweden and the UK (Björklund & Dunnett, 2007).

Although the idea that alteration of brain chemistry could have an effect on mood is now generally accepted by psychiatrists, this was not the case in the 1960s. So much so that in the introduction to his review 'The biochemistry of affective disorders' Alec

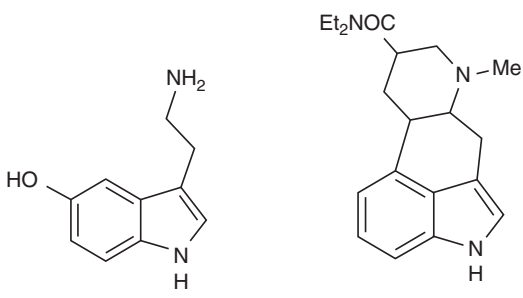

Figure 1.5 Chemical structures of 5-HT and LSD.

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Coppen stated: '*The title of this review would be regarded by some psychiatrists as provocative; they would relegate the biochemical concomitants of depression and mania to a secondary position and deny the biochemical changes have any place in the aetiology of these conditions*' (Coppen, 1967).

The preclinical development of new drugs in these early days was reliant on two fundamental approaches. One was to use medicinal chemistry to synthesize structurally similar compounds to an existing therapeutically active drug to mimic the known biochemical and behavioural actions of that compound with the hope that the new compound would have greater efficacy and possibly fewer adverse effects. The other was to examine the preclinical pharmacology of the known compound and integrate this information with the expanding clinical knowledge of this drug to try and understand its mechanism of action and again produce compounds acting similarly. This latter approach is termed translational and reverse translational pharmacology. This tended to work successfully until the 1970s as there were fewer regulatory controls on clinical investigations compared to today, and small experimental studies on patients could be conducted and information fed back to initiate further preclinical studies (Sjoerdma, 2008). Such studies are now impossible as small-scale 'look see' studies on patients are not permitted for ethical reasons. Nevertheless, greater day-to-day collaboration between preclinical and clinical psychopharmacologists can still be valuable and its loss in many academic centres is unfortunate. It has been suggested that its re-emergence would enhance the discovery process in both psychiatry and other therapeutic areas (Green & Aronson, 2012).

1.8.2 Depression and the Monoamine Hypothesis of Affective Disorders

The preclinical development of antidepressant drugs in the 1950s to 1980s followed the path of good clinical observation of unexpected therapeutic activity, followed by development of related drugs and greater understanding of their possible mechanism of action. Iproniazid was first discovered to be a MAOI by Zeller et al. (1952) and later reported to have an antidepressant action by Nathan Kline (Loomer et al., 1957), among others. This led to several companies synthesizing other hydrazine derivatives and the hypothesis that raising the concentration of brain monoamines (5-HT and noradrenaline) by inhibiting their breakdown by MAO would lead to an antidepressant action. The toxicity of hydrazines meant that most of these drugs were removed from the marketplace fairly soon after launch. As it happened, another class of drug, the TCA, started to appear at much the same time and these drugs rapidly replaced the MAOIs, although it took preclinical psychopharmacologists several years to clarify how they might be acting.

The first TCA (imipramine) was structurally related to the phenothiazines antipschotics (Figure 1.3) and was found empirically to act as an antidepressant. Structurally related compounds from other companies followed, but with little idea as to any possible mechanism of action. However, during the mid-1960s onwards there was the discovery that monoamines were inactivated by their reuptake into the nerve ending (Iversen, 1971) and that several drugs, but notably the TCAs, inhibited the noradrenaline and 5-HT reuptake pumps. Their potency at these uptake sites varied, with desipramine being relatively selective at the noradrenaline site, and clomipramine at the 5-HT site, while amitriptyline was equipotent at both sites (see Grahame-Smith & Aronson, 1992).

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These major observations, together with the suggestion that the amine-depleting drug reserpine (used to treat hypertension) could produce a depressive episode, resulted in the development of the 'monoamine hypothesis of affective disorders'. Basically, this stated that increasing monoamine function, either by inhibiting the enzyme inactivating monoamines and thereby increasing the monoamine concentration (MAOIs), or by blocking the uptake pump to increase synaptic concentration (TCAs), resulted in an antidepressant effect, while lowering monoamine concentrations (reserpine) could induce depression. Most TCAs inhibit the uptake of both 5-HT and noradrenaline, although the ratio of activity varies (dopamine uptake is generally little affected). The involvement of 5-HT in the antidepressant action of TCAs was championed in the UK (Coppen, 1967), while the importance of noradrenaline held sway in the USA (Schildkraut, 1965).

The finding by Coppen et al. (1963) that the antidepressant activity of a MAOI could be enhanced by administration of the 5-HT precursor L-tryptophan further strengthened the hypothesis, so much so that today the simplistic statement that antidepressants increase the *amount* of 5-HT in the brain can often be read in the popular press, even though it is nonsense as TCAs do no such thing.

The idea that making antidepressant drugs more selective at the 5-HT or noradrenaline uptake site might maintain the therapeutic action but decrease adverse effects (most TCAs had both antihistaminic and anticholinergic activity) resulted in the development of drugs that were more selective at either inhibiting noradrenaline or serotonin uptake. In the 1970s two drugs that were selective noradrenaline reuptake inhibitors entered the market. One, nomifensine, also inhibited dopamine reuptake, and while it had antidepressant activity it was withdrawn by the manufacturers in 1986 following reports of an association with haemolytic anaemia (Committee on Safety of Medicines, 1986). This association was largely identified through the 'Yellow Card', a UK system for recording adverse incidents with medicines. The second was maprotiline, which was discontinued in the UK in 2006. Interestingly, neither compound has the tricyclic structure. Drugs that are selective as serotonin reuptake inhibitors (SSRIs) entered the market during the 1980s and early 1990s and included fluoxetine, fluvoxamine, paroxetine and citalopram. These became extensively prescribed and remain widely used today. The SSRI drugs are clinically effective and safer in overdose than the TCAs. However, individual SSRIs show similar efficacy to each other and also to both the earlier non-selective drugs and also later drugs such as venlafaxine that have activity at both 5-HT and noradrenaline uptake sites (there is some evidence that certain antidepressants may be slightly more efficacious than others but the differences are marginal – for a further discussion see Cleare et al., 2015). Targeting a selective neurochemical site therefore predominantly produced more 'me-too' drugs in terms of postulated mechanism of action.

Although the monoamine hypothesis (increasing the synaptic concentration of monoamines) proved to be an effective marketing story, its weaknesses were apparent by the later 1980s. Firstly, later antidepressant drugs such as mianserin and iprindole had little effect on monoamine uptake, although they do have actions at monoamine receptors. Secondly, the TCAs and MAOIs could be shown to have a rapid biochemical effect in both rats and humans, but significant clinical improvement is often delayed for two to three weeks. Recent meta-analysis has challenged the idea of 'delayed' antidepressant action by showing that symptom improvement with SSRIs starts within one week of initiating treatment with the improvement building up over

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subsequent weeks (Taylor et al., 2006). The difference between this and the earlier view of delayed clinical effect probably reflects the sensitivity of methods used to measure change and how one defines a significant improvement. Nevertheless, the point remains that clinical improvement is slower than the changes seen in monoamine chemistry in animal models. Thirdly, administration of TCAs actually inhibits monoamine synthesis through a regulatory feedback inhibition process, and this is probably what was seen in the Sulser (1984) studies on β-adrenoceptor down-regulation that were some of the earliest to focus on the consequences of longer-term dosing in animals. It has been suggested that the initial changes in monoamine biochemistry may initiate longer-term mechanisms that result in the antidepressant effect, particularly as such adaptive mechanisms can be seen in other therapeutic areas (Grahame-Smith, 1997).

Despite the fact that the simple monoamine hypothesis of antidepressant action has now been abandoned (by psychopharmacologists at least) it is hard to deny that 5-HT is playing a role somewhere in the mechanism of many psychiatric drugs (Cowen, 2008). The top five selling drugs active on the CNS in the new millennium all modulated 5-HT function (Jones & Blackburn, 2002). The real problem for experimental psychopharmacology research is not merely that we still have relatively little understanding of how the drugs actually achieve their therapeutic effect, but rather that although the newer drugs such as the SSRIs produce fewer adverse effects, and have greater safety in overdose, the holy grail of producing a drug that has efficacy significantly greater than the older antidepressants such as amitriptyline has proved elusive. It is generally accepted that in the treatment of severe depression, ECT has the highest efficacy of all available treatments and experimental studies have been conducted to examine changes in brain neurochemistry produced when repeated electroconvulsive shocks (ECS) are given to rats (five to eight treatments spread out over a couple of weeks). Results demonstrated that ECS treatment actually produced many of the changes seen when antidepressant drugs were given, particularly altered 5-HT function. One notable change was in 5-HT_{1A} receptor function in rats, as this effect lasted for almost a month after the last ECS (Goodwin et al., 1985). However, despite this and related work, there remains no consensus as to the mode of action of ECT.

Some preclinical studies attempted to move away from the simple monoamine hypothesis. Such investigations included studies on peptides such as thyrotrophin-releasing hormone (TRH) and cholecystokinin (CCK), the β-adrenoceptor agonist salbutamol and β-adrenoceptor antagonist propranolol and drugs acting at 5-HT receptor subtypes, but none has resulted in clinically useful drugs, which does make one wonder whether the non-specific effect of uptake inhibitors releasing 5-HT onto all receptor subtypes is essential. One important recent area of investigation has been the role of glutamatergic drugs but whether this will lead to effective new drugs remains unclear (Naughton et al., 2014).

1.8.3 Antipsychotics and the Dopamine Theory

The situation with regard to the preclinical studies on the mechanism of antipsychotic drugs is, in some ways, less complex. The first clear indication that they might be acting through a defined neurochemical mechanism came in the report of Carlsson and Lindqvist (1963) that chlorpromazine and haloperidol, two effective antipsychotics but with

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markedly different chemical structures, both increased dopamine turnover, an effect that suggested dopamine receptor blockade. In addition, behavioural studies in rats observed that amphetamine-induced locomotor activity was antagonized by antipsychotic drugs. Since amphetamine was found to release dopamine in the brain, this strengthened the idea that antipsychotic action probably involved decreasing dopaminergic function.

The next major finding supporting this hypothesis was that there was a strong correlation between the potency of a wide range of antipsychotic drugs to act as antagonists at the dopamine D_2 receptor subtype and the average effective clinical dose (Enna et al., 1976). The idea that dopamine D_2 receptor antagonism resulted in anti-schizophrenic action in turn led some companies to focus on developing selective D_2 receptor antagonists (notably Astra with remoxipride and Janssen with risperidone). Although clinically effective, the failure of such drugs to treat schizophrenia more successfully than earlier drugs, at least in terms of treating both positive and negative symptoms, has helped to destroy any concept of dopamine selective activity being the only requirement. Indeed, the most successful drug for treatment-resistant schizophrenia is clozapine, a drug that has affinity for a wide range of dopamine and 5-HT receptor subtypes. More recent antipsychotics such as quetiapine also lack receptor specificity (Green & Aronson, 2012).

1.8.4 Drugs for Anxiety

The problem of producing a novel anxiolytic drug that was an improvement on those already on the market became evident after the late 1960s. Barbiturates were first discovered in the early years of the last century and available thereafter, with their use in the UK peaking in the 1950s. Their addictive properties and toxicity in overdose were known and seen as a major limitation to their use. The launch of chlordiazepoxide, the first benzodiazepine, was therefore a major step forward as the drug was effective, relatively safe and not thought to produce dependence problems. Its discovery resulted from re-testing in animal models a drug that had sat on the shelf of Hoffmann–La Roche for some time; another example of a highly successful drug that did not result from a structured drug discovery programme. Chlordiazepoxide was followed by the much more potent diazepam, and the shorter-acting nitrazepam; the latter was therefore marketed as a hypnotic. Preclinical studies indicated that the benzodiazepines acted via an action on the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Interestingly, both barbiturates and meprobamate also act through a GABAergic mechanism. What was fascinating was the identification of a specific benzodiazepine binding site on the GABA receptor (Braestrup & Squires, 1977), raising the possibility that the brain has an endogenous benzodiazepine. A variety of peptides and other compounds have been suggested to act at the site, the so-called endozepines (Farzampour et al., 2015). Moreover, the molecular biology of the $GABA_A$ receptor has revealed several functional subtypes with different distributions in the brain. The α_1 subtype is especially expressed in cortex and is the target of the first subtype-selective hypnotic zolpidem.

1.8.5 Drugs for Alzheimer's Disease

One neuropsychiatric disease where drug development was initiated as the result of preclinical observations is Alzheimer's disease. The first discovery that some of the clinical problems were neurochemical was the seminal report by David Bowen and colleagues of a

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loss of cholinergic neurons in the senile dementia brain (Bowen et al., 1976). This finding led to the use of cholinesterase inhibitors such as tacrine and rivastigmine. Post-mortem studies subsequently identified other neurotransmitter abnormalities including 5-HT and glutamate (Francis, 2009). These studies resulted in the clinical use of memantine, a glutamate NMDA receptor subtype antagonist. However, the fact that these approaches were merely symptomatic has resulted in most research now focusing on pharmacological ways to prevent the neurodegenerative changes, primarily the formation of plaques and tangles in the brain.

1.8.6 Animal Models in Psychopharmacology

A fundamental problem that runs through all preclinical psychopharmacology studies is the weakness of animal models. The validity of animal studies can be a problem in other therapeutic areas but is particularly troublesome in psychiatric disorders where there remains substantial ignorance of their causes and pathology.

Animal models can simplistically be divided into two basic types; those that can be used as screens to detect possible therapeutic value for a specific indication and those that try to mimic the clinical condition. Most early models were those for drug screening and to show responses to acute drug administration even though the drugs themselves are only clinically effective after longer-term administration. Acute tests include the Porsolt test for antidepressants (Porsolt et al., 1978) and its related tests, the elevated plus maze for anxiolytics (Cryan & Sweeney, 2011) and prepulse inhibition of the acoustic startle for antipsychotic drugs (Jones et al., 2011). The behaviour evoked in response to a provoking stimulus in these tests, given as it is to a 'normal' animal, probably involves different neuronal circuits and neuropharmacology from that required to treat a psychiatric disorder in the human brain. Furthermore, many screening animal models will only detect drugs that act through a specific neurochemical mechanism, whereas the symptoms of psychiatric disorders are many and this probably reflects multiple mechanisms. Consequently, novel compounds may not be detected. For example, SSRI drugs show up poorly in most animal models of anxiety (Cryan & Sweeney, 2011).

To try and deal with this problem there have been substantial efforts made to model psychiatric disorders. Psychopharmacology presents particular problems because, as Horrobin (2003) pointed out: '*An animal model of disease can be said to be congruent with the human disease only when three conditions have been met: we fully understand the animal model, we fully understand the human disease and we have examined the two cases and found them to be substantially congruent in all important respects.*' Ignorance of the causes and pathology of the major psychiatric diseases emphasizes that these conditions cannot be met. Models only partly replicate the full clinical condition or pathology of the disorder. In an attempt to deal with this problem, the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative recommended a battery of rodent behavioural tasks with translational relevance to most of the seven cognitive domains affected in schizophrenia. MATRICS also recommended a specific neuropsychological test battery to characterize these domains (Kern et al., 2008; Nuechterlein et al., 2008).

There is a need for new animal models that accurately reflect the pathophysiology of the disease, as emphasized by Spedding et al. (2005), and newer models of schizophrenia (Jones et al., 2011), anxiety (Cryan & Sweeney, 2011) and depression (Robinson, 2018) are available, albeit only reflecting some of the pathology, as might be expected.

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1.8.7 Conclusions Regarding Preclinical Research Studies

Since the late 1980s research approaches in psychopharmacology have changed from often undertaking 'look see' experiments to examine whether a compound might have an effect in an animal model (sometimes with no seriously developed hypothesis) or even sometimes clinically, to that of proposing a possible mechanism of action (for example, an interaction with a neurotransmitter receptor) and synthesizing further compounds that interact with that target site. This emphasis on target identification ('targetophilia') has produced novel drugs, and high throughput screening (HTS) has speeded up the process of identifying potentially useful new compounds. However, it has not enhanced the drug discovery process, and it may even have slowed the discovery process down as it '*requires a good understanding of target physiology and its integration with the target organ, with a hierarchical integration from in vitro cellular and functional tissue studies to animal models that reasonably predict human responses*' (Enna & Williams, 2009). In the case of CNS disorders, researchers were unable to meet this requirement 25 years ago, when targetophilia first became extensively used in the pharmaceutical industry, and are only modestly closer now. A single target approach will only work if the mechanism being targeted is the final step in the pathway that leads to the pathology. Given the complexity of psychiatric illness and evidence suggestive of multiple causative factors (both genetic and environmental), a final common pathway seems unlikely in most cases. Preclinical psychopharmacology has made enormous advances over the years, giving us greater understanding of the neurochemical changes produced by psychoactive drugs and suggesting possible mechanisms by which they produce their therapeutic effects. Nevertheless, a lack of understanding of the mechanisms involved in psychiatric disorders has meant that existing drugs are treating symptoms, not the underlying initiating factors. In terms of failure of new drugs, neuropsychiatry does not have a worse attrition rate than several other therapeutic areas companies still support and various new scientific approaches have been proposed to get the industry re-engaged with this vital area of public health (Green & Marsden, 2013).

To date, all drugs approved to treat depression and psychosis manipulate monoamine transmission, though some have additional actions. Developing drugs to treat depression and schizophrenia that have alternative mechanisms of action has proved disappointing with several notable failures including Group II metabotropic glutamate receptor ($mGlu_{2/3}$) agonists to treat schizophrenia (Li et al., 2015). One reason may be that trials recruit too broad a range of patients. People with both depression and schizophrenia almost certainly encompass subgroups with different neurotransmitter abnormalities. This argues that in clinical trials, and later in clinical practice, medications should be matched to different underlying disease mechanisms. For example, it may be that some people with schizophrenia have a primary dopaminergic abnormality and others a primary glutaminergic abnormality. The process of matching drugs to the presumed underlying pathophysiology is termed stratification. It requires the identification of reliable biomarkers (e.g. genetic, neuroimaging, electrophysiological, neurochemical) to identify underlying disease mechanisms and thereby predict response to specific medications. At present work adopting this approach is in very early stages but it appears an important avenue for future preclinical research and clinical practice. Drug development is discussed in detail in Chapter 2 of this book.

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1.9 The Legacy of the Psychopharmacology Revolution

In the first half of the twentieth century care for those with severe mental illness in North America, Australia, New Zealand and most European countries was largely provided by asylums. Underfunding, understaffing and overcrowding meant that standards of care were low despite the good intentions of many staff. Up to 1949 there were no effective treatments for major mental illness. Many patients in asylums displayed severe psychotic symptoms and behavioural disturbance (Norton, 1979). Medications that were available could only treat anxiety, provide sedation and help control disturbed behaviour. The introduction of antipsychotic drugs in the 1950s allowed mania and schizophrenia to be treated effectively for the first time and contributed to the demise of ineffective treatments including psychosurgery, insulin-coma treatment and ECT to treat schizophrenia.

The introduction of effective psychiatric drugs in the 1950s had widespread ramifications. It became apparent that scientific methodology was required to assess their clinical impact and this led to the development of RCTs in psychiatry. One of the earliest randomized trials in psychiatry compared lithium to placebo in the treatment of mania (Schou et al., 1954). This was a small study with less than 40 participants. Some were treated double blind but others received open treatment. The study utilized a cross-over design in which subjects received treatment with lithium and then treatment with placebo or vice versa. By the early 1960s several large double-blind randomized studies, with parallel treatment arms, had been published comparing phenothiazines to placebo in the treatment of schizophrenia (Adelson & Epstein, 1962; Casey et al., 1960; National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group, 1964). To allow the systematic assessment of treatment outcome in trials, symptom rating scales were developed as were rating scales to assess medication side effects. Today, RCTs are not only the benchmark for establishing the efficacy of pharmacological treatments, but also of psychological treatments and competing methods of service delivery. RCTs alone cannot answer all the questions regarding drug safety and furthermore they assess efficacy, i.e. the ability of a drug to treat a condition in ideal circumstances. Observational studies are necessary to assess effectiveness, i.e. how well a drug works in real-world clinical practice. Post-marketing surveillance plays a vital role in monitoring drug safety.

The introduction of new psychiatric drugs in the 1950s helped to reduce the stigma of mental illness. The fact that mental illnesses could be treated with medicines put them, to a degree, on a par with medical conditions such as diabetes and hypertension. The new treatments also served to generate hope among patients, families and mental health staff. Prior to the introduction of the antidepressants and antipsychotics in the 1950s, care in the asylums for those with severe mental illness often came down to containment. It is important to acknowledge that some people find the idea of having to take a medication to treat a mental health condition stigmatizing in its own right. Similarly, although many people find it helpful to know that there are biological factors at play in the genesis of a mental illness, if the concept is misunderstood it may incorrectly help foster a view that self-help is not possible.

The second half of the twentieth century saw a massive reduction in the number of psychiatric inpatient beds in many countries and the parallel development of community psychiatric services, a process termed deinstitutionalization. In England the number of

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psychiatric beds peaked at approximately 150 000 in 1955 and had fallen to around 22 000 in 2012 (The Kings Fund, 2015). In the United States the number of inpatients in state mental hospitals peaked at 559 000 in 1955 and had fallen to 57 000 by 1998 (Lamb & Bachrach, 2001). The causes of deinstitutionalization, and whether the introduction of the antipsychotics contributed, have been the subject of much debate. The two extremes are represented by the argument that the antipsychotics were 'wonder drugs' that almost single-handedly emptied the asylums versus the view that deinstitutionalization was solely a social phenomenon. Most authorities, including the authors, take an intermediate view regarding deinstitutionalization as the result of multiple factors of which the antipsychotics were one (Grob, 1991; Shorter, 1997). It is reasonable to suggest that the antipsychotics contributed in several ways. Their effectiveness in treating severe psychiatric symptoms (hallucinations, delusions, manic excitement, thought disorder and agitation) facilitated the discharge of some patients. They also allowed a greater proportion of hospital patients to engage and benefit from rehabilitation. Some patients in the community could be treated with antipsychotics without the need for admission. Finally, the antipsychotics probably played an indirect role by giving policymakers a rationale to move care from the asylums to the community, making this process more publicly acceptable and giving clinicians a greater confidence in providing community services.

Social factors were without doubt also an important contributor to deinstitutionalization. In both the USA and UK, a change in government policy aimed to drastically cut the asylum population and shift mental health care to the community. In addition, changes to mental health law meant that informal admission to psychiatric inpatient units became the norm. The introduction of Medicaid in the USA in 1965 provided a financial incentive to move care from the state-funded asylums to federally funded institutions including nursing homes and psychiatric wards attached to general hospitals (Gronfein, 1985). Additional factors that contributed to the closure of the asylums included increasing public awareness of scandals and poor care in asylums, recognition of the problems caused by long-term hospital admission, including institutionalization, and a greater appreciation among professionals of social and psychological treatments. Views on the success of community-care for the mentally ill vary and critics argue that deinstitutionalization was followed by an increasing population of people with mental illness in prisons, supported housing and forensic psychiatric units (Priebe et al., 2005).

The psychopharmacology revolution stimulated research into the biological nature of psychiatric illness and led to the creation of psychopharmacology as a discipline. For example, the introduction of the MAOIs and TCAs led to the monoamine theories of depression (Coppen, 1967; Schildkraut, 1965) and schizophrenia (Carlsson & Lindqvist, 1963) being proposed. Both theories of depression have been modified over time (e.g. Cowen, 2008; Howes & Kapur, 2009) and have faced criticism. The issue here is not to what extent they are right or wrong, but to emphasize that drug development led to theories being proposed that could then be tested in a scientific manner.

In summary, the psychopharmacology revolution changed the practice of psychiatry and led to the creation of psychopharmacology as a new scientific discipline. However, psychopharmacology is not without its critics or its problems as will be discussed in the following two sections.

1.10 Controversies in Psychopharmacology

Some of the most strident criticism of psychopharmacology, as well as drug treatment in other disease areas, has related to the actions of pharmaceutical companies. The role of pharmaceutical companies in developing new medications to treat psychiatric and medical disorders has helped revolutionize medicine over the last 50 years, improving quality of life for countless people. In many disease areas the advantages of pharmacological treatment are apparent in terms of increased life expectancy. The expertise and finance necessary to bring one new drug to market is huge, recently estimated at $1.2 billion (Adams & Brantner, 2010). As such, it is difficult to conceive further advances in drug development occurring without the involvement of the pharmaceutical industry.

A major problem affecting pharmacological treatment was that until fairly recently there was no requirement to register or publish the results of RCTs. Consequently, licensing decisions and systematic reviews could be based on a skewed evidence base because negative trials are less likely to be published. At its worst this could represent a drug company deliberately suppressing a negative study, but the problem also encompasses independent research groups whose priorities may lie in publishing positive studies rather than negative ones. In addition, journals are more likely to publish positive studies with the result that negative studies are often reported briefly or only as conference abstracts. To prevent this problem, clinical trials registries, such as Clinical .Trials.gov run by the United States National Library of Medicine, allow RCTs, industry sponsored or otherwise, to be registered, and the results made available within a short period of completion. In the United States and many other countries registration of Phase II to IV clinical trials is now mandatory. This has partly addressed the concern of unpublished trial data, although recent research shows that adherence to registry guidelines is far from perfect (Jones et al., 2013).

Other problems related to industry-sponsored research have included companies failing to make data available to independent researchers, controversy about the methodology and statistical analysis used in trials, industry promotion of drugs beyond their licence and failure to declare conflicts of interests by authors and researchers. These are all serious issues that are now being addressed. They apply to all branches of pharmacological research and not just psychopharmacology. Parallel issues apply to research on psychological treatments, but this has attracted less attention.

Some critics have argued that psychiatric drugs are overprescribed and do more harm than good (Gøtzsche et al., 2015). There is no doubt that some psychiatric medications have been used inappropriately. Examples include the overprescription of benzodiazepines leading to iatrogenic dependence (Lader, 2014) and the excessive use of antipsychotic drugs in nursing homes to manage behavioural disturbance (Tjia et al., 2012). However, one cannot generalize from these examples to all psychotropic prescribing and all psychiatric disorders. Many factors can drive the inappropriate use of psychiatric drugs. These include overpromotion by drug companies, an unquestioning approach by doctors to the information they receive from companies, a desire from some patients and relatives for a 'simple fix' for emotional distress and psychiatric problems, a widening of diagnostic criteria and clinicians applying diagnostic criteria too loosely so that an increasing proportion of individuals are deemed 'ill' and prescribed for. Lack of availability of psychosocial interventions may also mean that a pharmacological approach is the only intervention available to a clinician and patient. Public information, training for

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doctors, guidelines for company advertising of drugs and clinical guidelines all have a role to play in ensuring that prescribing is appropriate and evidence-based.

The introduction of evidence-based clinical guidelines has been a major development in recent decades leading to greater uniformity in the quality of treatment. Psychological treatments are first-line treatments for many psychiatric disorders including anxiety disorders and major depressive disorder that are of mild to moderate severity. However, critics of psychopharmacology often seem to lack awareness of the severity, persistence and disability associated with psychiatric illnesses such as schizophrenia, bipolar disorder and severe major depressive disorder that psychiatrists deal with every day, and of the benefits that can come from appropriate prescribing that is part of a comprehensive package of care that incorporates psychosocial treatments.

Another criticism levelled at psychopharmacology is that the evidence base supporting long-term treatment is flawed. Trials that support the long-term efficacy of psychiatric drugs usually have a continuation design in which those with an acute illness who respond to a drug are randomized to stay on that drug, or switch to placebo. It has been suggested that in some cases the switch from active drug to placebo may trigger a drug 'withdrawal' reaction which is misdiagnosed as a relapse; that is, in some patients the recurrent nature of mental illness may be partly an iatrogenic effect (Montcrieff, 2006). In the case of schizophrenia this has been linked to antipsychotics causing dopamine receptor supersensitivity. This hypothesis warrants further research; there is evidence of withdrawal effects with many psychiatric drugs and rebound psychosis has been recognized to occur with clozapine. However, a meta-analysis of randomized antipsychotic maintenance trials (trials in which stable patients with schizophrenia are randomized to continue or withdraw from their current antipsychotic) showed that the benefit of antipsychotics in reducing relapse was not affected by how quickly the antipsychotic was withdrawn in those randomized to placebo (Leucht et al., 2012). This contrasts to the findings of an earlier and less comprehensive analysis by Viguera et al. (1997) in which the risk of relapse was higher after abrupt discontinuation of oral antipsychotics compared to gradual discontinuation of oral antipsychotics or stopping depot injections. The Leucht et al. (2012) finding is not consistent with an iatrogenic explanation of relapse. Nevertheless, it does not rule out the possibility that a drug withdrawal effect may contribute to relapse in a minority of patients. It has also been argued that tolerance to the maintenance effect of antipsychotics develops over time. In support, Leucht et al. (2012) noted that the effect of antipsychotics in reducing relapse, compared to placebo, reduced with increasing study duration. However, as the authors point out, there are other explanations of this finding; it could reflect antipsychotic non-adherence which tends to increase with increasing duration of treatment, or that the severity of illness and potential for relapse varies between those enrolled in short-term and long-term trials. Ultimately, a scientific approach and further research is the only way to answer these and related questions.

In summary, psychopharmacology has attracted both criticism and controversy. Similar issues have been seen in many parts of medicine and other aspects of psychiatry, though this is not in any way to downplay these issues. Positive criticism is helpful and can lead to clinical and research issues being seen from a different perspective. Open discussion and continuing research, education and collaboration with other organizations and the public are among the important ways to deal with these areas.

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1.11 Current Problems Facing Psychopharmacology Research

Since the 1950s knowledge of CNS transmitter systems and their interplay with other bodily systems and genetics has increased at an incredible rate. It has been accompanied by the introduction of in vitro and in vivo techniques including the ability to image receptors and brain activity in living subjects. Unfortunately, this explosion of scientific knowledge has not been matched by the introduction of more effective psychiatric drugs. In particular, the efficacy of drugs to treat depression and schizophrenia (with the exception of clozapine) has not changed significantly since imipramine and chlorpromazine were introduced in the 1950s. The reasons for this are many but include the complexity of the CNS, deficiencies in current animal models used for preclinical research and weaknesses in the design of clinical trials including recruiting too broad a range of patients. Ideally in a clinical trial, one would aim to recruit a subset of patients on the basis of reliable genetic, neuroimaging or other biomarkers that were postulated to predict response to the drug being investigated. If the trial was successful, then similar stratification could also be adopted in clinical practice. Currently, the ability to target treatments in this way is in its infancy. A related approach is to develop drugs that target specific symptom domains of a clinical syndrome, for example cognitive dysfunction or primary negative symptoms in schizophrenia, and investigate putative treatments in samples enriched for the symptom domain in question. Another contributing factor to the paucity of new compounds is the relative underfunding of CNS research relative to other disease areas. When disability and economic burden are considered, neuroscience research is underfunded in comparison with research for cancer and coronary heart disease (Green & Marsden, 2013; Luengo-Fernandez et al., 2012).

The prospect for developing improved drugs for CNS disorders has taken a further setback in recent years as most major drug companies with an interest in this field have scaled back their research and development programmes or moved away from the area totally. This reflects the complexity and difficulty of developing new and more effective CNS treatments. The recent failure of a number of drugs in development, including glutamatergic drugs for schizophrenia, and the fact that most health services require increasingly strong evidence that new drugs offer advantages in efficacy or safety before approving use, has further weakened confidence in companies wishing to invest in research on psychiatric disorders. However, failures in drug development in the CNS are not clearly worse than in some other therapeutic areas (Green & Marsden, 2013).

Reduced investment in psychopharmacology research and development is particularly worrying given the high disability associated with CNS disease. Fineberg et al. (2013) estimated that in 2010 there were approximately 45 million cases of brain disorders in the UK, with an annual cost of €134 billion. This comprised 27% direct healthcare costs (i.e. cost of healthcare professionals, hospitalization, investigations, medication and other treatments), 27% non-medical direct costs (e.g. cost of social services and special accommodation) and 46% indirect costs (i.e. lost productivity due to work absence and early retirement). The five costliest disorders were dementia, psychotic disorders, mood disorders, addiction and anxiety disorders. The coming decades are likely to see an increase in the incidence and cost of brain disorders in the UK due to an increasing elderly population. For this reason, and to reduce individual

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suffering and to improve quality of life, there is a pressing need to develop new and more effective treatments, including new medications. This will require investment in translational neurosciences research and close collaboration between the healthcare sector and preclinical and clinical scientists (Green & Aronson, 2012).

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