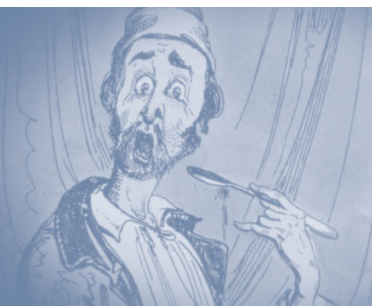


Developing Treatments



‘Melancholia’ and ‘Mania’

Up until the 20th century mental illness was chiefly divided into the categories of ‘melancholia’ and ‘mania’. ‘Melancholia’ equates with the modern diagnosis of depression. ‘Mania’ was used for what we call schizophrenia and the manic episodes of bipolar disorder. (Bipolar disorder is also known as manic depression).

Here we are focusing on the pharmaceutical treatment of these illnesses, rather than treatments such as bathing, electroshock or psychoanalysis. The story is largely one of frustration until the dramatic breakthroughs of the mid-20th century. Psychiatrists continue to debate issues surrounding psychopharmacology.

What is Depression?

Depression is the most common of all the psychiatric illnesses. It is now estimated that one in four of us will experience depression to some degree at some point in our lives. Depression is frequently referred to as the common cold of mental health.

Some people only suffer from mild depression. They feel low in mood and lose motivation. Things that interested them no longer bring them pleasure. Other people can spiral down from these beginnings to feelings of total hopelessness and suicidal thoughts.

People with only mild depression can have their lives blighted for years because their condition is not severe enough to prompt them to seek medical help. On the other hand people who suffer greatly can be treated successfully with antidepressants and return to full mental health.

What is Bipolar Disorder?

Bipolar disorder is also known as manic depression. Typically this illness is characterised by mood swings. Periods of depression alternate with 'manic' periods when the sufferer is on a high.

As with depression there are degrees of this illness. One sufferer may experience mild depression as described above. His or her manic episode may manifest itself as slight hyperactivity and increased creativity. Another person may endure severe depressions. Many with bipolar disorder do commit suicide. At the other end of the spectrum they experience psychotic episodes often accompanied by delusions. For example it is common for them to believe that they are the Virgin Mary or a famous person. By this stage they are so manic they cease sleeping and medical intervention is vital.

What is Schizophrenia?

Schizophrenics do not have a 'Jekyll and Hyde' personality split, which is a common misconception. Schizophrenia is characterised by 'negative' and 'positive' symptoms. Negative symptoms include emotional and social withdrawal, poor rapport and apathy. Positive symptoms include delusions, hallucinations, hearing voices, and feelings of persecution. Schizophrenics usually appear in the media for having committed violent acts. In fact they are far more likely to do harm to themselves than to others.

Early Treatments: Purgatives, Emetics and Bleeding

In the medieval period people frequently attributed mental illness to 'the snares of evil spirits'. Therefore sufferers often sought a spiritual cure, such as a visit to a shrine.

The most common medicinal treatments for mental illness, from the Middle Ages onwards, were to bleed the patient, give them a purgative or make them vomit. The herb, black hellebore, was used as a purge by Ancient Greek physicians. It was still being used in Victorian asylums.

In the 1600s Culpeper recommended the use of other substances such as the plant epithimum (or dodder vine). "It purges melancholy, as also cholera, it resists madness, and all diseases coming of melancholy, and therefore let melancholy people esteem it as a jewel".

"The use of hellebore, the art of the old doctors in healing the insane, seems to have been lost." (Anton Muller. 1824)



Photograph shows:

Bleeding Bowl, dated 1730. Bleeding, like purging and inducing vomiting, began as a treatment with the ancient Greeks. They believed that it was vital for health to keep the 'four humours' in balance. As blood was one of the humours, bleeding a patient was one way of restoring balance.

Drug Jar for Syrup of Epithimum, 1660-1725. The herbalist, Culpeper, said of syrup of epithimum (dodder vine) that "It purgeth melancholy".

Rock Crystal. The Elizabethans made a tincture from powdered rock crystal and took it to treat melancholy.

Victorian Trial and Error

In Victorian asylums, physicians were trying out drugs other than purgatives.

In the 1870s George Savage, Physician Superintendent to Bethlem Hospital, recorded the results of a range of medicinal treatments. The drugs he tried included morphine, chloral hydrate, hemlock juice, tincture of digitalis and emmenagogues (which brought on menstruation). He even tried claret mixed with sulphate of soda.

There were some successes. One lady was so improved by morphine that she would beg for it "on the evening of a ball". But there were far more cases where little, if any, improvement was observed.

Savage came to the conclusion that most drug treatment was futile. "I would say that insanity requires no special treatment medicinally...The moral treatment must for long, if not for ever, be the chief thing aimed at."

"The rashness of trusting to drugs alone will become more and more generally perceived."

(John Conolly, Treatment of the Insane without Mechanical Restraint, 1856)

The writings of two men provide an excellent insight into the Victorian practice. These individuals are George Savage, Physician Superintendent to Bethlem Hospital, (On the Treatment of Insanity, more especially by Drugs, 1878) and John Conolly (The Treatment of the Insane without Mechanical Restraints, 1856).



Photograph shows some of George Savage's suggested treatments:

Opium gum, in early 20th century specimen jar.

George Savage recorded: "Until recently opiates were looked upon as one of the sheet-anchors in the arrest of mental disease. Now we are more discriminating, and have to own that whereas some cases are relieved by opium some are not affected at all, whilst others are really injured by its use."

Morphine Sulphate tablets, around 1900 and early 20th century.

George Savage reported: "After trying opiates in several forms I have almost given up all preparations but morphia...I have given morphia in mania of several varieties, and rarely, if ever, with anything more than temporary benefit...In melancholia more benefit has followed, but not in all cases."

Choral Hydrate crystals, mid 20th century. **Chloral Hydrate tablets**, around 1900.

George Savage wrote: "Of all medicines recently introduced this has been the most largely used, and I fear that if the good results were compared with the evil done the latter would preponderate. Savage did however use it "in states of maniacal excitement...and have produced more or less quiet, but I cannot record a single case in which recovery seemed due to its use."

Claret & Bishop's Sulphate of Soda, early 20th century. "Last year we gave claret mixed with sulphate of soda in small doses at short intervals to several acute maniacs at the request of a French doctor, who said he had seen many such cases become

quiet under treatment; but after three weeks' trial, none of the patients being in any improved, we discontinued the treatment.”

Succus Digitalis (digitalis juice), late 1800s.

“Tincture of digitalis has a rapidly depressing effect, and produces quiet in some cases of acute mania; but the general health having failed under its use, I should hesitate to try it freely again in any cases of simple insanity...” Savage.

Succus Conii (hemlock juice), late 1800s.

Savage administered this drug with the juice containing one fourth part of ‘spirit’ (alcohol).



Liquid Ergot, mid 20th century. **Caulophyllum & Pulsatilla,** early 20th century.

Both these preparations are emmenagogues (medicines that bring on menstruation). Many of George Savage’s contemporaries believed that amenorrhoea (absence of periods) could cause insanity. Savage thought that: “It is not necessary that patients should always menstruate before they are discharged well, but I have greater confidence in the welfare of such patients as have successfully passed two periods after convalescing.”

Mackenzies Cod Liver Oil Emulsion, late 1800s.

John Conolly referred to “the recent extensive introduction of the use of the cod-liver oil into practice.” Conolly thought it beneficial.

Cantharadis Solution, early 20th century. This medicine both brings up blisters and is a counter-irritant (causes irritation when applied to the skin). Conolly wrote that “Blisters are occasionally useful”. He states that counter-irritants have been used “in some cases with striking effects, but often, also, with none...”

Drugs that transformed psychiatry: Chlorpromazine, Lithium & Imipramine

In the early 20th century the drugs used in psychiatry were the 'chemical straightjackets' such as opiates, bromides, and barbiturates that simply sedated patients.

In 1952 this all changed with the trials of **chlorpromazine**. Many pharmacy historians have regarded chlorpromazine as the single most important drug in the history of psychiatry. Its impact has even been compared with that of penicillin.

Chlorpromazine treated the symptoms of schizophrenic psychosis with less sedation than previous drugs. It began a pharmacological revolution because it demonstrated that drugs, not psychotherapy, could restore mental health.

Just as chlorpromazine brought relief to sufferers of schizophrenia, so **lithium**, launched in 1954, became the 'gold standard' treatment for bipolar disorder. It is still the most common treatment today as it both treats and prevents mood disorders.

Imipramine was developed by the Swiss pharmaceutical firm, Geigy. In 1955, researchers gave it to 40 depressed patients. The results were dramatically successful. Geigy had produced the first drug in the history of psychiatry that acted specifically against depression.

Photograph shows:

Barbitone Sodium tablets, 1930.

Quinalbarbitone Sodium tablets, mid 20th century.

These drugs are barbiturates. Barbiturates were introduced as powerful sedatives in 1903. They were widely used in psychiatry until the mid 20th century. This was because they had fewer side effects, and were less toxic than previous sedatives such as chloral hydrate. But, in even moderate amounts, they could produce a state similar to alcohol intoxication. They still only controlled the patient's behaviour rather than their symptoms.



Largactil (Chlorpromazine Hydrochloride), 2001

Chlorpromazine was synthesized in the early 1950s as compound 4560 RP. It was first used in anaesthesia. The surgeon Henri Laborit was looking for a substance that could

induce a state of 'artificial hibernation' by affecting the central nervous system. Laborit thought it might possibly have a use in psychiatry. A trial on 38 psychotic patients showed that it could not only calm the patient but also treat a whole range of their symptoms. These included hallucination, delusions, confusion, anxiety states and insomnia. Chlorpromazine was the first of a class of drugs called 'typical' antipsychotics. They work by blocking dopamine in the brain.

Lithium Carbonate, around 1991.

Lithium is a natural element. It can be found in mineral waters. Around 200 AD the Greek physician Galen prescribed alkaline spring baths for manic patients. In 1949 the Australian psychiatrist John Cade found that lithium calmed manic patients. In the early 1950s, Mogens Schou demonstrated that lithium had even more important value as a preventative treatment.

Imipramine, 2001.

Imipramine was the first of a class of drugs called 'tricyclic' antidepressants. Since then many more of these drugs have since been developed, with varying side effects. However, imipramine is still considered by many psychiatrists to be the gold standard of antidepressant therapy.

Some More Recent Developments

Seroxat and other SSRIs:

SSRIs (Selective Serotonin Reuptake Inhibitors) are a class of antidepressants developed in the 1970s. Doctors began to prescribe SSRIs widely in the 1990s. They have few side effects and also treat obsessive-compulsive and post-traumatic stress disorder.

Sodium Valproate:

Psychiatrists are now using anticonvulsant medication, first developed to treat epilepsy, in the treatment of bipolar disorder. No-one is sure why these medications prove a successful mood regulator. Sodium Valproate is an anticonvulsant that is often prescribed when lithium does not relieve symptoms.

Olanzapine:

Olanzapine is one of group of drugs labelled 'atypical' antipsychotics. It was approved for treatment of schizophrenia in 1996. In 1999 it was also approved to treat patients with bipolar disorder who are experiencing psychotic episodes. Scientists do not know

exactly how olanzapine works. It may work by blocking receptors of several neurotransmitters (chemicals that nerves use to communicate with each other) in the brain.



Photograph shows:
Seroxat (Paroxetine), around 1992.

It is not precisely clear how SSRIs like Seroxat affect depression. Serotonin is a brain chemical (neurotransmitter) that is associated with depression. SSRIs seem to relieve symptoms of depression by blocking the reabsorption (reuptake) of serotonin by certain nerve cells in the brain. This leaves more serotonin available in the brain. As a result, this enhances the sending of nerve impulses (neurotransmission), and this in turn improves mood.

Epilim (Sodium Valproate), around 2001.

It is not definitely known why medication like this, developed for epilepsy, works for bipolar disorder. But there are theories. For one thing, there is a connection between bipolar disorder and seizure disorders. The psychotic experience that may accompany bipolar disorder can resemble some nonconvulsive seizures. For example, bipolar hallucinations can be accompanied by an 'aura', similar to epileptic auras. Also there is a disturbance of the normal electrical activity in the brain in both bipolar disorder and seizure.

Zyprexa (Olanzapine), around 2002.

'Atypical' medications, such as Olanzapine, are less likely than 'typical' antipsychotics to cause 'extrapyramidal symptoms' (EPS). EPS can include tremor, the need for constant movement, involuntary muscle movements in the face, and difficulties with speech. Zyprexa's low incidence of EPS makes it popular with users. It has the added benefit of helping individuals think more clearly and learn new information and skills more easily.

So Why Non-Compliance?

The 'drugs revolution' of the 20th century may have freed patients from their symptoms, but other issues have arisen.

Drug treatments for schizophrenia have side-effects. These include weight gain, drowsiness, blurred vision and social withdrawal. For this reason many sufferers cease taking their medication (are non-compliant). They become 'revolving door' patients, continually readmitted to hospital. One way around this is to give schizophrenics monthly 'depot' injections such as Depixol. Controversially, the NHS is considering paying patients when they receive a 'depot'.

People with bipolar disorder are often non-compliant in order that they can enjoy the creativity that comes with a 'manic' episode. This is particularly true of those in creative professions, such as the musician Kurt Cobain. Some maintain that his non-compliance was a factor in his suicide in 1994.

Depixol Injection (Flupentixol Decanoate), around 2001.

Depixol is injected into the patient's muscle, for example into the buttock. Because it is long-acting it is invaluable in treating chronic patients who have difficulty with compliance. 'Depot preparations' like Depixol are also used if immediate relief is required, rather than tablets that take time to take effect. An example of such a situation is if a patient is threatening to harm him or herself, or others.

Crisis Card for sufferers of Bipolar Disorder, 2007.

Produced by the 'MDF-the Bipolar Organisation'. Note that the first step listed is 'Medication' for both 'when going high' and 'when depressed'.



‘Cosmetic Psychopharmacology’ – The Future?

Prozac was approved in 1987. It inspired the term ‘cosmetic psychopharmacology’, first used in 1990. ‘Cosmetic’ refers to the fact that Prozac can be taken just to increase feelings of well being rather than treat illness (depression). Prozac has been described as making people feel ‘better than well’. The same has been said of St John’s Wort.

Prozac’s main market is proving to be people who want to feel ‘better than well’. It is unusual for people with a psychiatric illness to seek a particular treatment. In contrast, those with no diagnosis of depression specifically request Prozac.

This drug has been described as “as socially acceptable as spring water”. It has therefore removed much of the stigma of mental illness. However, does the future of psychiatry include making well people happier?

“People want to try it. If you tell them they’re not depressed they say, ‘Sure I am!’”
(Newsweek, 1990)

Prozac (Fluoxetine), around 1997 and 2001.

Fluoxetine was patented by Eli Lilly in 1975. The company considered bringing it out initially as a weight loss drug. Then in 1988 they launched fluoxetine in the United States as Prozac, as a drug for depression.

St John’s Wort (*Hypericum perforatum*), around 1996.

Dr James Giannini wrote in his article ‘The Case for Cosmetic Psychiatry’, Psychiatric Times, June 2004: “A feeling of overall well-being, not quite realized in daily pursuit of the mundane, can sometimes be produced with St John’s Wort...in people without depression.”