

Unrecognised Facts about Modern Psychiatric Practice

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No known biological causes

There are no known biological causes for any of the psychiatric disorders apart from dementia and some rare chromosomal disorders. Consequently, there are no biological tests such as blood tests or brain scans that can be used to provide independent objective data in support of any psychiatric diagnosis.

A simplistic biological reductionism has increasingly ruled the psychiatric roost... [we have] learned to attribute mental illness to faulty brain chemistry, defects of dopamine, or a shortage of serotonin. It is biobabble as deeply misleading and unscientific as the psychobabble it replaced.

Andrew Skull, Professor of History of Psychiatry, Princeton University, in *The Lancet*

There are two dominant myths with respect to the origins of mental health conditions. The first is that changes in mood can be traced to chemical imbalances. The second is that genes play a central role in the onset of mental disorders. We will review the lack of evidence for the chemical imbalance theory under 'Myth of the chemical imbalance' later in this document, and so here we will focus on the genetic hypothesis.

Genetics¹

Twenty years ago when the Human Genome Project was up and running there was great anticipation of finding singular gene mutations (or causes) for most emotionally or cognitively related problems. This was inspired by a few interesting discoveries related to what are now known as the organic brain diseases. Perhaps the best-known example is Huntington's disease. This is caused by a gene carried on chromosome 4 that destroys brain cells on the frontal lobes, leading to impairments in cognitive functioning. But these clear cut cases in the realm of mental health, are very much the exception. Most genetic influences on disease are greatly more complicated than those early pioneers of the genome project could have dreamed. For instance, in the realm of psychiatry there is no known gene or clear genetic variants for around 97% of all the mental disorders now contained in the current DSM and ICD. And even where genes may be implicated in disorders like bi-polar disorder and schizophrenia, research now reveals such mind-boggling complexity that nothing definitive can be said about 'this causing that'.

A central complicating factor is our growing understanding of epigenetics. Modern genetics now broadly accepts that it is virtually impossible to understand how our biology works outside the context of our environment. To put the new genetics in the simplest terms, virtually no neurological and psychological disorders have been demonstrated to result from the mutation of a single gene. Rather they are now known to involve molecular disturbances that implicate multiple genes and the signals that control their expression.² In other words, the popular idea that so-and-so gene causes so-and-so mental trait has been surpassed by the notion that it is interactions between our genes and their environment that actually shape us. This is because we now know there to be thousands of molecules attached to our DNA that can literally turn our genes on and off. These molecules, or 'epigenetic markers' as they are more technically known, actually alter and develop as an individual adapts to their environment.

The equation therefore runs something like this: because our environment affects these molecules, and because these molecules can turn our genes on or off, the environment can no longer be seen as irrelevant to how our genes determine our functioning and development.

Studies of rats have illustrated this point well. Baby rats born to mothers who rarely licked their pups where given to foster mothers who were very affectionate (who licked them a lot). Dissection revealed that the affectionately raised rats had brain characteristics different to those receiving little affection: the former possessed more of the neuron receptors considered crucial steppingstones in slowing down the

production of stress hormones. In short, a stretch of DNA, serving as a switch for a gene related to these neural receptors, had been suppressed in the less-affectionately raised rats. The conclusion is that adult personality differences related to stress weren't determined by genes inherited from their biological mothers, but were an outcome of how they were raised as pups.³

The same groups of researchers performed a related study on human beings, which analysed the brains of 36 people post mortem. Twelve of these people had died of natural causes, while the rest (24) had committed suicide. And of the 24 suicide victims, 12 of these had been abused as children, whereas the other 12 had not. When the brains of these three groups were compared, the brains of those in the group that had suffered childhood abuse shared the same pattern of fewer receptors linked to stress hormones. Their brains, via epigenetic changes, had reacted to the environmental abuse – leading them to grow in a direction different to brains receiving environmental care.⁴

Studies like these show that genes can be ‘switched on or off’ by molecules that are themselves altered by environmental factors.⁵ We know, for example, that there are two genes strongly associated with hereditary breast cancer (BRCA1 and BRCA2). But we also know these genes are responsible for only about 10 per cent of all breast cancers (and that only about a further 10%-20% of breast cancers are related to any kind of gene or variant). This means that most women who develop breast cancer may not be hereditarily disposed to do so.⁶ But even if they are hereditarily disposed, it also means they won’t necessarily develop the condition. As the American Society for Clinical Oncology (ASCO) asserts, woman with a 75% chance of developing breast cancer may remain perfectly healthy, while a woman with a 25% chance of developing breast cancer may eventually develop the disease.⁷ Again, the presence of the relevant gene alone is not enough to account for the disease’s onset. The environment influencing epigenetic factors play a crucial role.

In the face of such complexity, research into the genetics of ‘mental disorders’ such as depression, schizophrenia and bi-polar has continued. In 2003, for example, a study was published in the journal Science that asked why stressful experiences lead to depression in some people but not in others. After analysing 847 patients over time, it found that those who had one or two copies of a gene variant that interfered with serotonin transport were three times as likely to develop depression if subjected to certain stressful life events, like losing a job or getting divorced. This study was thought to provide evidence of a gene-by-environment interaction, in which an individual’s response to environmental stresses is moderated by his or her genetic makeup.⁸ This finding generated a great deal of excitement, until another study, published a few years later, tried to replicate these findings. This next study assessed over 14,000 people via a meta-analysis of over 14 studies. But the conclusion it reached, dampen the previous excitement: ‘This meta-analysis yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression in men alone, women alone, or in both sexes combined.’⁹

Another major study that scanned the genetic sequences of 20,000 normal people and then compared them with the sequence of 10,000 patients with schizophrenia revealed that over 10,000 different gene variants could have a role in the onset of schizophrenia. And this study did not take the findings of epigenetics into account (the environmentally susceptible molecules that interfere with these genetic variants).¹⁰

While it is important to support work in genetics, it is also important to be clear about what this work so far allows us to say. Given the ever-complex developments in fields like epigenetics, all we can do today is embrace a position littered with caveats: where genetics play a role in our mental lives, they do so via a given, yet-defined, constellation of genes that may predispose a person to an unknown degree of vulnerability to developing a given form of mental distress if other social or psychological conditions trigger it, and if environmentally influenced epigenetic factors permit it. Such tentativeness is now slowly trickling through to the mental health establishment, as can be seen from the World Health Organisation’s recent official statement on the causes of depression:

Depression is a complex disorder which can manifest itself under a variety of circumstances and due to a multiplicity of factors... biological (genetic and biochemical), sociological (stressors) and psychological (development and life experiences) factors interact to produce a picture of depression. Research during the last fifty years indicates that there is no single factor which can explain the cause for depression.¹¹

The WHO does not say genes or biochemical imbalances cause depression. All it says is all anyone can say: of course our biology is implicated in mental distress, just as it is implicated in any emotional, physical or mental state that is experienced as either positive or negative. But precisely how it's implicated, and precisely to what degree, we do not really know.

CEP supports ongoing research into the biology of all human behaviours, emotions and traits. It also believes in respecting our current level of knowledge and not going beyond what the research permits us to say.

Myth of the chemical imbalance

Psychiatric drugs have often been prescribed to patients on the basis that they cure a 'chemical imbalance'. However, no chemical imbalances have been proven to exist in relation to any mental health disorder. There is also no method available to test for the presence or absence of these chemical imbalances.

In 1965, in a paper published in the American Journal of Psychiatry, the NIMH's Joseph Schildkraut put forward a chemical imbalance theory of affective disorders. It was he said, 'at best a reductionistic oversimplification of a very complex biological state'.¹² He also stated that at the time of writing there was no evidence to support or disprove the theory.

Schildkraut's theory inspired a generation of researchers to test it. Although Schildkraut thought that norepinephrine was the neurotransmitter most likely to be deficient in those diagnosed with depression, researchers quickly turned their attention to serotonin. In 1969, Malcolm Bowers, of Yale University, was one of the first to investigate whether depressed patients had low levels of serotonin metabolites in their cerebrospinal fluid. He studied eight depressed patients who had all been exposed to antidepressants and announced their 5-HIAA levels were lower than normal but not 'significantly' so.¹³

In 1971 researchers at McGill University said they too failed to find a 'statistically significant' difference in the 5-HIAA levels of depressed patients. They also failed to find any correlation between 5-HIAA levels and the severity of depressive symptoms.¹⁴

In a follow up study in 1974 Bowers concluded: 'Depressed patients who had not been exposed to antidepressants had perfectly normal 5-HIAA levels'.¹⁵ In the same year, Joseph Mendels and Alan Frazer, researchers at the University of Pennsylvania, looked at the evidence that had lead to Schildkraut to put forward his theory and concluded: 'The literature reviewed here strongly suggests that the depletion of brain norepinephrine, dopamine or serotonin is in itself not sufficient to account for the development of the clinical syndrome of depression'.¹⁶

Later, in 1984, NIMH investigators again studied the low-serotonin theory and lead investigator James Maas and others discovered 5-HIAA levels varied widely in depressed patients. They drew the conclusion: 'Elevations or decrements in the functioning of serotonergic systems per se are not likely to be associated with depression'.¹⁷

This last point is in agreement with a recent and definitive review of all basic antidepressant research published in the New England Journal of Medicine. As it stated: 'Numerous studies of norepinephrine and serotonin metabolites in plasma, urine and cerebrospinal fluid, as well as post-mortem studies of the brains of patients with depression, have yet to identify the purported deficiency reliably'.¹⁸ In other words, and to quote the leading journal The Pharmacological Basis of Therapeutics, the data for the neurotransmitter hypothesis of mood disorder 'are inconclusive and have not been consistently useful either diagnostically or therapeutically'.

The absence of supporting evidence has led to a professional 'crisis of faith' in the chemical imbalance theory, as some of the following comments testify:

- 'Many neuroscientists no longer consider a chemical imbalance theory of depression and anxiety to be valid.' (Dr David D. Burns, Professor of Psychiatry, Stanford University)
- 'Chemical imbalance is sort of last-century thinking. It's much more complicated than that.' (Dr. Joseph Coyle, Professor of Neuroscience at Harvard Medical School)

- ‘After decades of trying to prove [the chemical-imbalance theory], researchers have still come up empty-handed.’ (Marcia Angell, former editor of The New England Journal of Medicine).
- ‘Despite pseudoscientific terms like “chemical imbalance” nobody really knows what causes mental illness. There’s no blood test or brain scan for major depression.’ (Dr Darshak Sanghavi, clinical fellow at Harvard Medical School)
- ‘We do not know the aetiology of really any of the mental disorders at the present time.’ (previous Director of Research at the American Psychiatric Association)
- ‘Research has yet to identify specific biological causes of any of these [mental] disorders.’ (U.S. Congressional Report, entitled: The Biology of Mental Disorders; New Developments in Neuroscience)
- ‘The results of decades of neurotransmitter-depletion studies point to one inescapable conclusion, low levels of serotonin, norepinephrine or dopamine do not cause depression.’ (Professor Irving Kirsch, Harvard Medical School)
- ‘We still don’t know the relationship between biology and the mental disorders.’ (Carol Bernstein previous president of the American Psychiatric Association)
- ‘Patients have been diagnosed with chemical imbalances, despite that no test exists to support such a claim, and that there is no real conception of what a correct chemical balance would look like.’ (Dr David Kaiser Psychiatric Times)
- ‘As a scientific venture, the theory that low serotonin causes depression appears to be on the verge of collapse. This is as it should be; the nature of science is ultimately to be self-correcting. Ideas must yield before evidence.’ (Dr Jonathan Rottenberg, Psychology Today)
- ‘A simplistic biological reductionism has increasingly ruled the psychiatric roost... [we have] learned to attribute mental illness to faulty brain biochemistry, defects of dopamine, or a shortage of serotonin. It is biobabble as deeply misleading and unscientific as the psychobabble it replaced.’ (Andrew skull, Professor of History of Psychiatry, Princeton University, Lancet)¹⁹

Although scientists have been testing the chemical imbalance theory’s validity for over 40 years – and despite literally thousands of studies – there is still not one piece of direct evidence proving the theory correct. The chemical imbalance theory, in relation to any mental health disorder is thus unsubstantiated, yet a societal belief in chemical imbalances, largely owing to effective pharmaceutical marketing, remains prevalent today.

Diagnostic system lacks validity

Psychiatric diagnostic manuals such as the DSM and ICD (chapter 5) are not works of objective science, but rather works of culture since they have largely been developed through clinical consensus and voting. Their validity and clinical utility is therefore highly questionable, yet their influence has contributed to an expansive medicalisation of human experience.

The DSM (Diagnostic and Statistical Manual of Mental Disorders) is the book that lists and defines all of the mental disorders believed to exist. In May 2013 its 5th edition was published (entitled DSM-5), amid considerable controversy. Some central criticisms of DSM-5 were summarised in an online petition that went live in 2012, protesting its publication. It was endorsed by over 50 organisations, including The British Psychological Society, the Danish Psychological Society and the American Counseling Association. The arguments stated that DSM-5:

1. By lowering the diagnostic thresholds for warranting a diagnosis, may lead to more people being unnecessarily branded mentally ill.
2. By including many new disorders that appear to lack scientific justification, there will be more inappropriate medical treatment of vulnerable populations (children, veterans, the infirm and the elderly).
3. By deemphasizing the sociocultural causes of suffering, biological causes will continued to be wrongly privileged.

The petition concluded: 'In light of the growing empirical evidence that neurobiology does not fully account for the emergence of mental distress, as well as new longitudinal studies revealing long-term hazards of psychotropic treatment, we believe that these changes pose substantial risks to patients/clients, practitioners, and the mental health professions in general'.²⁰

One of the more controversial changes in DSM-5 is that under certain circumstances grief can now be classified a symptom of mental disorder. While previous editions excluded bereaved people from being diagnosed with a major depressive disorder, DSM-5 has removed that exclusion. This means that as early as two weeks after the death of a loved one, if a person experiences deep sadness, loss, sleeplessness, crying, inability to concentrate, tiredness and low appetite, they can be diagnosed with depressive disorder. Critics argue that this will inevitably lead to many more thousands (perhaps even millions) of people be diagnosed and medicated unnecessarily. This pathologisation of grief has been strongly criticised by over 100,000 grievers worldwide,²¹ in over 100 critical articles in the world press, in two eloquent pieces in *The Lancet* and in one in the *New England Journal of Medicine*.²² Despite this widespread opposition, the DSM-5 decision stands.

Criticisms of the DSM are not just reserved for DSM-5. The entire DSM project (developed cumulatively over consecutive editions) is now under sustained attack. For example, we now know from extensive interviews with the creators of its previous editions (DSM-IV and DSM-III), that its construction was far less rigorous than many had assumed. For example, while DSM III listed 265 disorders (most of which still exist in DSM-5 largely unaltered), we also know that most these were established on the basis of scant and largely inconsistent research. As the Chairman of DSM III, Robert Spitzer, put it:

For many of the disorders that were added, there wasn't a tremendous amount of research, and certainly there wasn't research on the particular way that we defined these disorders.²³

As a key member of his taskforce, Theodore Millon, echoed:

*There was very little systematic research, and much of the research that existed was really a hodgepodge – scattered, inconsistent, and ambiguous. I think the majority of us recognized that the amount of good, solid science upon which we were making our decisions was pretty modest.*²⁴

Without solid data to guide them, they relied upon reaching consensus among themselves about whether to include new disorders and, if so, how they should be defined. As another taskforce member, Donald Klein, states:

*We had very little in the way of data, so we were forced to rely on clinical consensus, which, admittedly, is a very poor way to do things. But it was better than anything else we had... If consensus were not reached, then the matter would be eventually decided by a vote.*²⁵

The centrality of this voting or ‘consensus method’ has greatly undermined the manual’s legitimacy, casting suspicion upon its vast expansion – from 106 disorders in 1950 to around 370 today (counting the appendix inclusions and subdivisions). Critics point out that this vast expansion could occur because it is easier to ‘vote’ new disorders into existence than it is to scientifically discover them.²⁶ Critics have also suggested that the DSM’s rapid expansion, coupled with its lowering of thresholds as to what constitutes mental illness, has progressively and wrongly brought more and more human experience under psychiatric jurisdiction, creating the illusion of a psychiatric epidemic (if DSM-based estimates are to be believed, 1 in 4 of us suffer from a mental health disorder in any given year).²⁷

Critics further point out that this expansion has helped provide sanction and impetus to vaulting psychotropic prescription rates; rates amplified by decades of pharmaceutical industry marketing, physician and departmental funding, as well as research and regulatory ‘capture’.²⁸

In April 2013 Thomas Insel, the president of the National Institute for Mental Health (NIMH), the largest funding body for mental health research globally, stepped up the criticism of DSM by declaring that the ‘NIMH will be re-orienting its research away from DSM categories...[because the DSM’s] weakness is its lack of validity’. As he continued:

*Unlike our definitions of ischemic heart disease, lymphoma, or AIDS, the DSM diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure. In the rest of medicine, this would be equivalent to creating diagnostic systems based on the nature of chest pain or the quality of fever.*²⁹

Insel proposes we replace the DSM with a system that he hopes will someday be better grounded in biological research. Whether Insel’s solution is viable or not, his central point is nevertheless important: the NIMH is moving away from the DSM because it was not founded on any solid research base.

The DSM vs ICD in the UK

Chapter 5 of the ICD (International Classification of Diseases) is the WHO’s alternative to the DSM. Many British psychiatrists have argued that as we use the ICD in Britain, British psychiatry is largely exempt from these criticisms. This position is flawed for two reasons.

Firstly, the DSM has been highly influential in British psychiatry – both clinically and in terms of guiding research. In fact, the DSM has guided nearly all psychiatric research into mental disorders in Britain. Furthermore, the NICE guidelines in the UK dedicate as much time to the DSM as the ICD and actually recommend the use of the DSM over the ICD for particular conditions including depression.³⁰ In short, the DSM has significantly influenced British research and practice.

Secondly, the argument that ‘we use the ICD therefore we are exempt’, seems to assume that the ICD is a superior manual. The facts suggest it is not. Firstly, it contains almost as many disorders as the DSM, including those such as female orgasmic disorder, caffeine related disorders, stammering, stuttering,



reading disorder, transexualism, oppositional defiance disorder, non-compliance with treatment, and so on. Furthermore, the ICD's research base is no more solid than the DSM's. After all, the ICD was constructed via the very same voting and consensus system dominating the DSM. Finally, both ICD and DSM teams worked closely to cohere both manuals to safeguarded against there being two radically different diagnostic manuals within psychiatry.

CEP supports an independent review into the utility and validity of manuals such as the ICD (Chapter 5) and DSM. We believe both manuals have led to the unnecessary medicalization of people on a comprehensive scale, which has led, in turn, to more people needlessly suffering the stigma of being labeled mentally ill, and to more being unnecessarily prescribed potentially harmful psychiatric drugs. CEP believes such widespread and unjustified medicalisation, and thus medicating, of human experience is creating more human and societal problems than it is solving.

Psychiatric drugs cause altered mental states

Just like other substances that affect brain chemistry (such as illicit drugs), psychiatric drugs produce altered mental states. They do not ‘cure’ diseases, and in many cases their mechanism of action is not properly understood.

These drugs, when they do have effects, work more like substances that temporarily alter our state of mind, such as caffeine or cannabis. These pills, in other words, don’t cure us – they simply change us. They can throw us temporarily into a foreign state of mind, into an altered version of who we are.³¹

People have used psychoactive drugs to change their state of mind for centuries, but during the 20th century, a new range of psychoactive drugs were introduced, including drugs that we now call ‘antidepressants’ and ‘antipsychotics,’ along with benzodiazepines like Valium and Librium. At first, these new drugs were largely thought of as at best soothing tonics that changed a person temporarily rather than cured a disease. As the psychiatrist and researcher Dr. Joanna Moncrieff put it: ‘They weren’t understood to act upon underlying diseases like they are today. They were seen as drugs that would pep you up or calm you down. They were accepted as sticking plasters or up-lifters that might at best be able to suppress symptoms for a period, but never were they seen as reversing a disease state.’³²

However, this view started to alter in the 1960s and 1970s as the idea was postulated that such drugs may well reverse a disease state. By the 1980s this view had become widely accepted. These drugs, it was now believed, worked by correcting, or helping to correct, underlying biological abnormalities assumed to produce particular psychiatric symptoms. This dominant model of how psychiatric drugs work can be called the ‘disease-centred model’; a model reflected in the names of the major drug classes. For example, antidepressants are believed to reverse biochemical pathways that give rise to symptoms of depression, and antipsychotics are thought to act on the mechanisms that produce psychotic symptoms.

Despite the lack of evidence supporting the disease-centred, it has been widely embraced by psychiatry. The reasons for this are complex, but two are of note. Firstly, the disease-centred model is consistent with psychiatry’s vision of itself as a medical specialism just like any other, with drugs that target and cure underlying illnesses. Promoting this view has been crucial for psychiatry given its historical struggle for full medical status. Secondly, the disease-centred model has legitimised the wide-scale manufacturing and dissemination of psychiatric medications by the pharmaceutical industry (i.e. if mental illness is caused by a physical malfunction, and these pills correct that malfunction, then their consumption is both necessary and justified).

Despite the enormous financial and professional investment in the disease-centred model, there does exist an alternative model. This alternative is the ‘drug-centred model’ which stresses that psychiatric drugs are, first and foremost, psychoactive drugs; drugs that induce varied and unpredictable physical and mental states that do not constitute a ‘cure’. This alternative model is now widely embraced in psychology, psychotherapy and other mental health specialisms. There are also numerous psychiatrists whose research is also consistent with this view.^{33, 34}

The view that psychiatric drugs cure an underlying pathology is greatly weakened when we acknowledge that the introduction of new specific drugs has not improved the prognosis of major psychiatric disorders, which is the opposite of what you would expect if the drugs were truly combatting disease. As Dr. Moncrieff points out: ‘The failings of the medico-biological approach to madness and mental distress are obvious and frustrating to many psychiatrists as well as other mental health professionals and service users. Medical doctors, including psychiatrists, are beginning to become more aware of the compromising influence of the pharmaceutical industry over medical and psychiatric practice and many are enthusiastic about non-drug-based interventions. Some are concerned about the possible damage

that may be done by long-term psychiatric drug use, both physical and psychological, the latter by inducing dependence and chronicity, and aggravating certain psychological symptoms.³⁵

The view that psychiatric drugs cure an underlying pathology is also greatly weakened by observing the effects such drugs have upon healthy individuals. According to the disease-centred model drugs should only exert their effects on disordered states of mind. But extensive research shows that all psychiatric drugs have psychoactive effects on healthy volunteers^{36, 37}. Benzodiazepines, for example, have calming effects on people whether or not they are complaining of anxiety, and the emotionally numbing effects of antidepressant can also be observed in ‘healthy’ people who take them.

Adopting a drug-centred model has various advantages. Firstly, acknowledging that psychiatric drugs create altered mental states allows the doctor and patient to have an honest, open discussion about the advantages and disadvantages of the various drug effects. Some effects may be useful in the short term, for example the calming effect of an antipsychotic during acute psychosis. However, this same effect may have undesirable consequences on other aspects of a patient’s life, for example while driving a car.

A drug-centred model is also more likely to lead to discussion of long-term adverse affects. This approach acknowledges that the drug is providing symptom relief through its psychoactive action rather than curing a physiological problem – and that, over time, the psychoactive action can cause undesirable changes to brain chemistry (see Long-lasting negative effects on cepuk.org) leading to a range of negative effects. The drug-centred model therefore provides a rationale for selective rather than continuous drug use.

A drug-centred model also imposes a duty on the psychiatric research community to produce relevant, unbiased information about the range of effects that psychiatric drugs can have on all bodily systems, both during short-term and long-term use. At present, the influence of the disease-centred model keeps the full range of effects of many drugs hidden, and therefore neither doctors nor patients can make fully informed decisions about the risks and benefits of using them.

While assumptions have been made about the disease-targeting properties of psychiatric medications, the reality is that the mechanism of action of many of these drugs is poorly understood. For example, while SSRIs medications are believed to block the re-uptake of serotonin, thereby increasing the levels of serotonin in the synapse, contemporary neuroscience has failed to provide any link between serotonin deficiency and any mental disorder.³⁸

Likewise, antipsychotics are known to block dopamine pathways in the brain. This realisation led to the development of the dopamine hypothesis, which posits that psychosis (or schizophrenia) is caused by over-activity of dopamine. However overall, research fails³⁹ to prove that there is any specific link between dopamine and psychosis; an alternative explanation is that antipsychotics cause neurological suppression which in turn reduces the intensity of psychosis symptoms.

Ritalin and other stimulants are prescribed to millions of adults and children diagnosed with ADHD. Stimulants affect dopamine along with other neurotransmitters, and as a consequence of this it has been suggested that ADHD is related to dysfunction in the dopamine system. However, there is no convincing evidence that ADHD is caused by dopamine abnormalities.⁴⁰ Moreover, the characteristic effects of stimulants, which include improved attention at low doses, occur in everyone regardless of whether or not they have an ADHD diagnosis.

There is no evidence linking the pharmacological action of any class of psychiatric drug with the targeting of a disease process. CEP believes that the disease-centred model of psychiatric drug action is misleading, harmful and unsupported by the facts. A drug-centred model is an essential starting point for considering the cautious and safe use of drugs in mental health services.

Antidepressants have no benefit over placebo

Studies have found that antidepressants have no clinically significant benefit over placebo pills (inert pills) in the treatment of mild to moderate depression, while they provide some benefit for severe depression, at least in the short term. Recent research also suggests that antidepressants may be associated with a risk of increased mortality, at least among the elderly.

For the majority of people taking antidepressants (around 85%) they work, on average, no better than placebo pills (inert pills). This conclusion has been demonstrated by numerous ‘meta-analyses’ – these are studies that have gathered together all of the clinical trials that have, in this case, attempted to assess whether antidepressants work better than placebo pills.

Professor Irving Kirsch (Harvard Medical School) conducted the most noted and perhaps definitive of such analyses. Kirsch’s meta-analysis included all the major clinical trials of SSRI antidepressants – both those that were published and the nearly 40% that were withheld from publication by the pharmaceutical companies who sponsored or conducted them (the withheld trials largely showed negative results). After pooling all the data, Kirsch’s analysis revealed that the vast majority of people who took the antidepressant experienced, on average, no clinically significant improvement over those who took the placebo.⁴¹

Kirsch’s findings have been consistently replicated. Walter Brown, professor of psychiatry at Brown University, co-authored two studies that independently analysed the same set of clinical trials surveyed by Kirsch. His results confirmed that for a small minority of patients (the most severely depressed – 10–15%), antidepressants were shown to have some minor benefits over sugar pills. But for mildly/moderately depressed patients (85–90% patients) antidepressants offered no advantage over placebos, alternative therapies, or even moderate exercise.⁴²

A further, major meta-analysis commissioned by the NHS, and published this time in *The Lancet*, again showed the difference between placebos and antidepressants is so modest, that for mild to moderate depression antidepressants they were not worth having at all.⁴³ As the lead author of the study stated: ‘Our widespread comparative meta-analysis of antidepressants showed pretty clearly, that the difference between the published and unpublished studies of antidepressants in children, was that for the published trials, all the drugs worked, while for the unpublished trials none of the drugs worked.’⁴⁴

In addition to working no better than placebos for most patients, antidepressants are now coming under serious scrutiny for their potentially damaging effects, such as increasing the likelihood that a person who takes them will become chronically ill. As Giovanna Fava, an Italian psychiatrist, writes, ‘The time has come for debating and initiating research into the likelihood that psychotropic drugs actually worsen, at least in some cases, the progression of the illness which they are supposed to treat.’⁴⁵

Researchers at the University of Louisville Medical School, who have recently explored this area, have highlighted evidence that ‘in some individuals, persistent use of antidepressants may be pro-depressant’. One such researcher, El-Mallakh, suggests that SSRIs may in fact deplete serotonergic function, causing a ‘chronic and treatment-resistant depressive state... in individuals who are exposed to potent antagonists of serotonin reuptake pumps [SSRIs] for prolonged periods’.⁴⁶ Such concerns are

compounded by research that associates antidepressants with a significantly higher risk of relapse following cessation of the drug vs a placebo. A meta-analysis performed researchers at by McMaster University (Ontario), for instance, shows that the risk of relapse in the three months following discontinuation was 21.4% for placebo but rose to 43.3% for SSRIs and 55.2% for SNRIs.⁴⁷ The authors suggest that this increase in relapse is caused by the brain's 'pushback' against the effects of antidepressants; an effect that renders the person more susceptible to depression following cessation.

Alarmingly, three recent, large, prospective epidemiological studies have found that, even after controlling for depressive symptoms, antidepressant use is associated with an increased risk of death in the elderly. In one study the number of deaths per year caused by antidepressants was estimated to be 10.8 out of 1000 elderly people taking antidepressants.⁴⁸ Another study estimated that antidepressants caused the deaths of roughly 5 in 1000 elderly women per year.⁴⁹ It is possible that these higher rates of mortality are specific to the elderly; however current research cannot rule out the possibility that the cumulative effects of antidepressants on the integrity of the brain and peripheral processes could shorten the lifespan considerably.

Furthermore, several UK charities that support patients withdrawing from psychiatric drugs report that many people suffer from severe, long-term withdrawal effects after coming off antidepressants. In some cases these symptoms are reported to last for years and can be very debilitating. There is also evidence of long-term or perhaps permanent sexual dysfunction following discontinuation of SSRIs.⁵⁰

Despite what the evidence tells us, antidepressants are still being prescribed at a remarkable rate. There were over 50 million prescriptions of antidepressants dispensed in England in 2012 alone. Furthermore, while most of the antidepressant effect is now understood to be a 'placebo effect' we also know that between 40% and 70% of people taking them (depending on the study consulted) experience side effects. The NHS's list of side effects include: sickness, dizziness, low sex drive, erectile dysfunction, blurred vision, diarrhoea, dry mouth, feeling agitated or shaky, loss of sleep, excessive sweating, and in some cases increased confusion and suicide ideation.⁵¹

There are many other negative effects that have also been noted, but which rarely (if ever) are included in official lists of 'side effects'. For example, in 2009 a team of researchers at The University of Oxford assessed over 38 patients who had taken SSRIs antidepressants for periods between 3 and 48 months. Their results were published in the British Journal of Psychiatry, and what follows constitutes a summary:⁵²

- Most participants described a general reduction in the intensity of all the emotions that they experienced, using words like 'dulled', 'numbed', 'flattened' or completely 'blocked', to capture how they felt.
- A few participants described feeling no emotions at all, while others reported their emotional experience had become more 'cognitive' or 'intellectual'.
- A few described how the emotions that were at times present seemed 'unreal', 'fake' or 'artificial'. Almost all participants, paradoxically, described a reduction in their positive emotions, including a reduction happiness, enjoyment, excitement, anticipation, passion, love, affection and enthusiasm.

- Most participants also described feeling emotionally detached from their surroundings. Most also described feeling detached from other people. Specifically, they felt reduced sympathy and empathy, and felt detached during social interactions. Many participants also described an emotional detachment from their friends and family, including their partner or children.
- Almost all participants described not caring about things that used to matter to them. They cared less about themselves, about other people and about the consequences of their actions. Not caring could have both helpful and unhelpful consequences: it could reduce the sense of pressure and stress, but it could also increase the likelihood that important tasks were neglected.
- Many participants felt they just did not care as much about the consequences to themselves of their behaviour. A few participants went further, mentioning thoughts of self-harm or suicide that they related to their emotional detachment and numbness. Many participants reported being less sensitive or courteous towards other people, having reduced concern for others' feelings, and reduced concern about other peoples' opinions of them. Some participants described being less concerned or even unable to care about responsibilities in their everyday lives.
- All participants experienced a reduction of intensity or frequency of negative emotions. Most considered that at some stage the reduction in negative emotions was beneficial to them. Although this reduction was usually at some stage a relief, many participants also reported it impaired their quality of life. Participants described the need to be able to feel negative emotions when appropriate, such as grief or concern. Some were unable to respond with negative emotions, such as being unable to cry when it was appropriate to do so.
- Some participants felt their personality had changed in some way. They felt they were not the person that they used to be. Participants also reported that specific aspects of their personality, and, in particular, emotional aspects, had been changed or lost. Some participants believed that at times their antidepressant had made them behave out of character.

A separate study published in 2014, confirms much of the above. It surveyed 1,829 antidepressant consumers, and confirmed these drugs have widespread adverse psychological effects. For instance, and as a result of taking antidepressants, 62% of patients reported suffering from 'sexual difficulties'; 60% from 'feeling emotionally numb'; 52% reported 'feeling not like myself'; 42% experienced a 'reduction in positive feelings'; 39% reported 'caring less about others'; 55% experienced 'withdrawal effects'; while over 50% aged 18 to 25 reported suicidal feelings. On the up side, 82% reported that the drugs had helped alleviate their depression, however, as we also know from meta-analyses, that figure was mostly due to the placebo effect. The authors state: 'While the biological side-effects of antidepressants, such as weight gain and nausea, are well documented, the psychological and interpersonal effects have been largely ignored or denied. [Yet] they appear to be alarmingly common.'⁵³

Antidepressants have effects, but mostly they have placebo effects, side effects and negative effects such as those described above. There is no research to date confirming that they have any kind of 'curing' effect, and there has yet to be discovered a clear biological 'disease' that these pills target and treat. Furthermore, various studies suggest that long-term use of antidepressants may in fact increase the chronicity of depression and lead to higher mortality rates, at least among the elderly.

Worse long-term outcomes

There has been little research on the long-term outcomes of people taking psychiatric drugs. The available studies suggest that all the major classes of psychiatric drugs add little additional long-term benefit, and for some patients they may lead to significantly worse long-term outcomes.

Today, biological psychiatry works on the premise that its medications fix a physical problem and that, in many cases, psychiatric drugs should be taken indefinitely by patients. However, as we still do not understand the biology of mental disorders, the validity of both of these beliefs is highly uncertain. The following series of studies throw into serious doubt the value of long-term drug treatment and the belief, still held by many psychiatrists, that mental disorders are usually lifelong, chronic conditions.

Between 1945 and 1955, prior to the introduction of Thorazine (chlorpromazine), three studies in the USA and one in the UK provide insight into the unmedicated outcome of patients diagnosed with schizophrenia.

In an NIMH study of patients newly diagnosed with schizophrenia, 62% of first-episode psychotic patients admitted to Warren State Hospital from 1946 to 1950 were discharged within 12 months. At end of three years, 73% were living in the community.⁵⁴ A further study of 216 schizophrenia patients admitted to Delaware State Hospital from 1948 to 1950, reported that 70% were successfully living in the community six years after initial hospitalisation.⁵⁵

Hillside Hospital in Queens, New York, also reported that of the 87 patients discharged in 1950, just over half did not relapse in the following four years.⁵⁶ In studies of schizophrenia patients in England, 33% enjoyed a complete recovery, and another 20% a social recovery, which meant they could support themselves and live independently.⁵⁷

Following the introduction of Thorazine in 1955, the California Department of Mental Hygiene conducted the only large scale study that compared discharge rates for first episode patients treated with and without drugs. In 1961 they reported that of the 1,413 first-episode schizophrenia patients hospitalized in California in 1956, 88% of those who weren't medicated were discharged within 18 months, compared to 74% of those treated with a neuroleptic. Researchers concluded, 'Drug-treated patients tend to have longer periods of hospitalization... The untreated patients consistently show a somewhat lower retention rate.'⁵⁸

In 1956 the NIMH established the Psychopharmacology Service Centre which developed a trial design for testing psychotropic drugs. Psychiatrists and nurses would use this trial to measure numerically the characteristics of the disorder to be studied. The severity of all the symptoms would be also measured to achieve a total 'symptom' score. A drug would be counted as 'effective' if it reduced the score significantly over a six-week period. Some concerns were raised about this method at the 1956 NIMH conference. Here the researcher Joseph Zubin warned, 'It would be foolhardy to claim a definite advantage for a specified therapy without a two to five year follow-up. A two year follow-up would seem to be the very minimum for the long-term effects.'

Following the Psychopharmacology Service Centre's nine-hospital trial of neuroleptics in 1961, hundreds of smaller trials were conducted and produced evidence that the drugs reduce symptoms over the short-term better than a placebo. The NIMH conducted a one year follow-up study of their nine hospital trial and at the end of one year, patients who were treated with placebo upon initial admission to hospital, 'were less likely to be rehospitalised than those who received any of the three active phenothiazines'. This was the first indication that whilst the drugs were effective over the short-term they might make

people more vulnerable to psychosis over the long-term. For example, only 7% of those on a placebo at the start of the study relapsed, while a full 65% of those taking more than 500 milligrams of chlorpromazine relapsed, before the drugs were withdrawn.⁵⁹

Psychiatrists J. Sanbourne Bockoven and Harry Solomon of Boston Psychopathic Hospital compared the outcomes in the pre-Thorazine era and the post-Thorazine era in a retrospective study. It showed that 45% of the patients treated at Boston Psychopathic Hospital in 1947 did not relapse in the five years following discharge; 76% were successfully living in the community at the end of that follow-up period. In contrast, only 31% of patients treated in 1967 with drugs at a Boston Community Health Center remained relapse-free for the next five years, and as a group they were much more ‘socially dependent’ than those in 1947. Bockoven and Solomon wrote, ‘Rather unexpectedly, these data suggest that psychotropic drugs may not be indispensable. Their extended use in aftercare may prolong the social dependency of many discharge patients.’⁶⁰

With this in mind the NIMH funded further studies in the 1970s. In the first, conducted by William Carpenter and Thomas McGlashshan, 35% of the non-medicated patients relapsed within a year after discharge, compared to 45% of drug-treated patients. Medicated patients suffered more from depression, blunted emotions, and retarded movements.⁶¹

The results of the three year study in 1978 by Maurice Rappaport of the University of California in San Francisco found 27% of newly diagnosed schizophrenia patients treated initially without drugs in the hospital relapsed in the three years following discharge, compared to 62% of the medicated group. Of the 41 patients initially treated without antipsychotics, 24 remained unexposed to antipsychotics at end of three years, and this group had by far the best overall outcomes. Rappaport wrote, ‘Are there schizophrenics for whom drugs may be unnecessary or contraindicated? Our findings suggest that antipsychotic medication is not the treatment of choice, at least for certain patients, if one is interested in clinical long-term improvement.’⁶² As Rappaport and Bola continued, ‘We think that the balance of risks and benefits associated with the common practice of medicating nearly all early episodes of psychosis should be re-examined.’⁶³

Loren Mosher’s Soteria project in the late 1970s treated 82 patients over 12 years. The treatment was in a homelike environment (Soteria), where antipsychotics were minimally used and the idea was to treat patients as individuals, with dignity and respect (42% were never exposed to antipsychotics; 39% only on a temporary basis; 19% on a continual basis). At the end of two years, the Soteria patients had ‘lower psychopathology scores, fewer (hospital) re-admissions, and better global adjustment’ than those treated conventionally with antipsychotics.⁶⁴

In the late 1950s and early 1960s Vermont State Hospital discharged 269 chronic schizophrenics into the community. During the 1980s, Courtenay Harding interviewed 168 of these patients. She found 34% of schizophrenia patients were completely off medications and had recovered; she wrote it was a ‘myth’ that schizophrenia patients ‘must be on medication all their lives’ and ‘it may be a small percentage who need medication indefinitely’.⁶⁵

In two studies, in 1969 and 1978, the World Health Organisation outcomes for schizophrenia patients in developing countries were much better than outcomes in the U.S. and other developed countries. In developing countries, 15.9% of patients were continuously maintained on neuroleptics, compared to 61% of patients in the developed countries. In this cross-cultural study, the best outcomes were associated with low medication use. In 1997 patients from the first two studies were interviewed again and researchers concluded that in countries where patients hadn’t been maintained on antipsychotics earlier in their illness, the majority had recovered and were doing well fifteen to twenty five years later.⁶⁶

Between 1974 and 1983 Martin Harrow, a psychologist at the University of Illinois College of Medicine, enrolled sixty-four schizophrenia patients in a long-term study. He then periodically assessed them, producing the most up-to-date study we have today. His report was published in 2007. Outcomes for

schizophrenia patients at the end of 15 years were as follows: 40% of unmedicated patients were classed as 'recovered' compared with 5% of medicated patients; 44% of unmedicated patients were classed as 'fair' compared with 46% of those medicated; while 16% of patients who were off medication were classed as 'poor' compared with 49% of medicated patients.

This finding was further reinforced by a study released in 2013 by the Dutch researcher Lex Wunderlink. Wunderlink tracked 103 patients who, after a first episode of psychosis, were given an antipsychotic for six months and then randomly assigned to one of two groups. Patients in the first group discontinued or reduced the dose of their antipsychotic drug, while those in the second group continued with a standard maintenance dose. After seven years the first group (which stopped or reduced the drug) had a 40.4% recovery rate while the second group (those who continued taking the antipsychotic) had a rate of only 17.6%.

In the pre-drug era, natural recovery rates from depressive episodes were also high. In the 1960s and early 1970s prominent psychiatrists described unipolar depression as fairly rare and having a good long-term course.

However, though patients taking antidepressants were getting better they were not improving significantly beyond patients treated with a placebo, and in the 1960s some European psychiatrists reported that the long-term course of depression in their drug-treated patients was actually worsening. Dutch physician J. D. Van Scheyen looked at the two groups over five years. He wrote, 'more systematic long-term antidepressant medication, with or without ECT, exerts a paradoxical effect on the recurrent nature of the vital depression. In other words, this therapeutic approach was associated with an increase in recurrent rate and a decrease in cycle duration... Should [this increase] be regarded as an untoward long-term side effect of treatment with tricyclic antidepressants?'⁶⁷

In 1990 a long-term NIMH study compared imipramine (a tricyclic antidepressant) with psychotherapy and a placebo. The 'stay well' rate was highest for cognitive therapy group (30%), and was lowest for the imipramine group (19%).⁶⁸ In 1994, Dr. Giovanna Fava alerted psychiatry to the possibility that antidepressants were turning depression into a chronic disorder and were as problematic over the long-term as neuroleptics and benzodiazepines. He wrote, 'I wonder if the time has come for debating and initiating research into the likelihood that psychotropic drugs actually worsen, at least in some cases, the progression of the illness which they are supposed to treat.'⁶⁹

Ross Baldessarini at Harvard Medical School, through a meta-analysis conducted in 1997, reported that 50% of patients withdrawn from antidepressants relapse within 14 months. He concluded that the longer the exposure to the drug, the greater the relapse rate.⁷⁰

In 2008, researchers at Ottawa University discovered that no good quality randomized trials exist comparing long-term outcomes in antidepressant-treated patients and never-medicated patients and therefore, randomised trials, 'provide no guidance for longer treatment'.⁷¹

A Dutch study published in 2000 looked at the outcomes after ten years of 222 people who suffered a first episode of depression. This showed that 76% of those who were not treated with a drug recovered, vs 50% who were prescribed medication.⁷²

A six-year NIMH funded study at the University of Iowa where researchers found depressed people who were medicated were three times more likely to suffer a cessation of their principal social role, and seven times more likely to become incapacitated than those who didn't get treated.⁷³

In 2006, Michael Posternak, a psychiatrist at Brown University studied what untreated major depression might look today. His findings showed that old epidemiological studies were not so inaccurate at all and considered why the six-week trials of the drugs had been misleading. He reported that 22% of non-medicated patients recovered after one month; 67% within six months; and 85% within a year. He

wrote, ‘If as many as 85% of depressed individuals who go without somatic treatment spontaneously recover within one year, it would be extremely difficult for any intervention to demonstrate a superior result to this’.⁷⁴

These studies together throw into serious doubt the belief that the long-term use of psychiatric drugs is good for the individual and society. Since the chronic nature of mental illness has yet to be established, there is no scientific justification for the lifelong use of psychiatric medications. Indeed there is now compelling evidence that such long-term use may be highly disadvantageous. This in turn leads to a more troubling possibility: that if there is any ‘chronicity’ in mental disorders then this may actually be an artifact of the medications themselves.

Long-lasting negative effects

Psychiatric drugs can have long-lasting effects on the brain and central nervous system, particularly when taken long term, which can lead to physical, emotional and cognitive difficulties.

All psychiatric medications effect the brain's functioning. For example, SSRI antidepressants block the removal of the neurotransmitter serotonin from the synapses; antipsychotic drugs suppress and block dopamine neurotransmission; and benzodiazepines amplify GABA neurotransmission, which in turn suppresses overall brain function.

As all psychiatric drugs have specific biochemical effects, over time other neurotransmitter systems react to these effects and broader changes begin to occur in the brain and in mental functioning. In his 2001 paper, 'Psychiatric drug-induced Chronic Brain Impairment (CBI): Implications for long-term treatment with Psychiatric Medication', Peter R. Breggin describes one such effect as 'chronic brain impairment' (CBI). He describes it as being 'associated with generalized brain dysfunction manifesting itself in an overall compromise of mental function'.

The symptoms of this syndrome include: cognitive deficits (often first noticed as short-term memory dysfunction and impaired new learning), difficulty with attention and concentration, apathy, indifference (or an overall loss of enjoyment and interest in life activities), affective dysregulation (including emotional lability), loss of empathy, increased irritability and finally a lack of self-awareness about these changes in mental function and behavior.

He comments, 'It is difficult to estimate what percentage of patients will develop CBI after years of exposure to psychiatric drugs. In my clinical experience, nearly all patients who remain on these chemical agents for many years will develop some symptoms of CBI. If the patient is taking multiple psychiatric drugs for years at time, in my experience CBI is always marked'.⁷⁵

Breggin argues that 'medication spellbinding' (or intoxication anosognosia) leads those affected to underestimate the degree of his (or her) drug-induced mental impairment. It also causes them to fail to recognise how the drugs may be changing their mental state or behavior. Patients may think that the drug is having no impact or that it is having some beneficial effect. While in extreme cases, typified by drug-induced euphoria or mania, individuals believe that they are functioning better than ever, when the drug is in fact mentally impairing them.⁷⁶

How does psychiatry address these problems? As early as 1995 the psychologist David Jacobs had noted that many psychiatrists seemed indifferent toward adverse drug effects. He wrote that, in medical and scientific papers, adverse drug reactions were usually reported as isolated events that neither impinged upon other people nor upon the individual's overall life.⁷⁷ Today this position is contradicted by mounting evidence suggesting that adverse drug effects are both prevalent and destructive, especially in long-term use. For instance, there is evidence showing that standard neuroleptics, over the long term, increase the likelihood that a person will become chronically ill (see below).

This outcome is particularly problematic when considering that such medications also cause a wide range of side effects, including neuroleptic malignant syndrome, Parkinsonian symptoms, and tardive dyskinesia. Patients maintained on standard neuroleptics increase their risk of developing blindness, fatal blood clots, heat stroke, swollen breasts, leaking breasts, impotence, obesity, sexual dysfunction, blood disorders, painful skin rashes, seizures, diabetes, and early death.⁷⁸

In his speech at the 2008 meeting of the American Psychiatric Association, Martin Harrow concluded that 'patients with schizophrenia not on antipsychotic medication for a long period of time have significant better global functioning than those on antipsychotics.' Between 1975 and 1983 he had assessed 64

young schizophrenics and periodically thereafter, his results suggested that, ‘those on antipsychotics had a much lower recovery rate, and were much more likely to have a uniformly poor outcome.’⁷⁹ This finding was further reinforced by a study released in 2013 by the Dutch researcher Lex Wunderlink. Wunderlink tracked 103 patients who, after a first episode of psychosis, were given an antipsychotic for six months and then randomly assigned to one of two groups. Patients in the first group discontinued or reduced the dose of their antipsychotic drug, while those in the second group continued with a standard maintenance dose. After seven years the first group (which stopped or reduced the drug) had a 40.4% recovery rate while the second group (those who continued taking the antipsychotic) had a rate of only 17.6%.

Turning to benzodiazepines, in 1998 Breggin wrote: ‘The benzodiazepines have for several decades been recognized in literature and clinical practice for their capacity to cause mental and behavioral abnormalities. The benzodiazepines can produce a wide variety of abnormal mental responses and hazardous behavioral abnormalities, including rebound anxiety and insomnia, mania and other forms of psychosis, paranoia, violence, antisocial acts, depression and suicide. These drugs can impair cognition, especially memory, and can result in confusion.’⁸⁰

A similar view was echoed by British investigators in 1991: ‘Both psychomotor and cognitive functioning may be impaired, and amnesia is a common effect of all benzodiazepines.’⁸¹ Researchers began to ask whether, in the long-term, benzodiazepines worsen the symptoms they are supposed to treat. In the 1990s Karl Rickels of the University of Pennsylvania School of Medicine reported that when long-term users had withdrawn from benzodiazepines they ‘became more alert, more relaxed, and less anxious, and this change was accompanied by improved psychomotor functions.’⁸² In 2007, French researchers surveyed 4,425 long-term benzodiazepine users and found 75 percent were ‘markedly ill to extremely ill, with significant symptomatology, major depressive episodes and generalized anxiety disorder often with severity and disability’.⁸³ Reports showed long-term benzodiazepine use causes emotional distress, cognitive impairment as well as impaired self-insight.⁸⁴ A review of the relevant literature by Australian scientists in 2004 concluded, ‘long-term benzodiazepine users were consistently more impaired than controls across all cognitive categories and the higher the intake, dose and period of use (of benzodiazepine), the greater the risk of impairment.’⁸⁵

Furthermore, withdrawal support organisations in the UK report numerous examples of individuals reporting severe physiological and psychological symptoms for months and sometimes years after withdrawing from benzodiazepines. Professor Heather Ashton, a UK expert, confirms in The Ashton Manual that many people take 6-18 months to recover, and sometimes considerably longer.⁸⁶

Evidence from many sources confirms that selective serotonin reuptake inhibitors (SSRIs) can also cause adverse drug reactions ranging from manic psychoses, agitated depression and obsessive preoccupations to violent, ‘abnormal’ behavior and increased suicidal ideation.

In 1993 Teicher et al. suggested nine possible mechanisms by which antidepressants (including SSRIs) induce or exacerbate suicidal tendencies.⁸⁷ Since then, additional studies have established a clear link between increased suicidality and antidepressants, leading to black box warnings in the US.⁸⁸ In addition investigators have reported that long-term use is associated with memory impairment in problem solving activities, loss of creativity and learning deficiencies. ‘Our field’, confessed Dr Maurizio Fava et al in 2006, ‘has not paid sufficient attention to the presence of cognitive symptoms emerging or persisting during long-term antidepressant treatment... These symptoms appear to be quite common.’⁸⁹

In 2009, a team of researchers at Oxford University undertook the first qualitative study of patient experiences of emotional side effects of SSRIs. The study provides robust evidence that some individuals taking SSRIs experience significant emotional symptoms and they strongly attribute it to their antidepressant.⁹⁰

In 2012 a study considered antidepressants and cognitive health across 383 post-menopausal women. It concluded that antidepressant use is associated with subsequent cognitive impairment and called for further research into role of antidepressants in the depression-dementia relationship.⁹¹

Some withdrawal support organisations in the UK report that over fifty percent of their enquiries now relate to difficulties experienced by individuals trying to withdraw from antidepressants. Severe withdrawal symptoms often last for months, and in some cases several years, often devastating lives in the process.

CEP supports independent initiatives to explore the long-term effects of psychotropic medications. Right now the evidence, although not conclusive, strongly suggests that long-term usage is ultimately disadvantageous for most people and very damaging for some.

Negative effects are often misdiagnosed

Psychiatric drugs can have effects that include mental disturbance, suicide, violence, and withdrawal syndromes. These can be misdiagnosed as new psychiatric presentations, for which additional drugs may be prescribed, sometimes leading to long-term use of multiple different psychiatric drugs in the same person.

All classes of psychiatric drugs can cause negative effects both as a consequence of taking the drug as directed and upon withdrawal from it. Sometimes these negative effects can be very severe and long-lasting (see ‘Long-lasting negative effects’ on the CEP website). Often these negative effects can mimic the disorder for which the drug was originally prescribed, or cause new psychiatric symptoms, which are then misdiagnosed as a new disorder. This can lead to instances where the original dosage is inappropriately increased, or new drugs are added. This often results in the potentially harmful use of multiple drugs, known as polypharmacy.

Severe negative effects

Antidepressants are the most commonly prescribed psychiatric drug in the UK, with over 50 million prescriptions dispensed in England in 2012 alone. Antidepressants are known to cause numerous negative effects, some of which are mild and short-lasting. However the link between SSRI-type antidepressants and abnormal behavior, including violence and suicide, is now firmly established. In his review of the literature in 2003 Dr. Peter Breggin writes:

‘Evidence from many sources confirms that selective serotonin reuptake inhibitors (SSRIs) commonly cause or exacerbate a wide range of abnormal mental and behavioral conditions. These adverse drug reactions include the following overlapping clinical phenomena: a stimulant profile that ranges from mild agitation to manic psychoses, agitated depression, obsessive preoccupations that are alien or uncharacteristic of the individual, and akathisia. Each of these reactions can worsen the individual’s mental condition and can result in suicidality, violence, and other forms of extreme abnormal behavior.’⁹²

One key symptom which experts believe contributes to this type of behavior is akathisia, described as an ‘an inner sense of unease, unrest, and dysphoria. It can result in an inability to stand, sit, or lie still, and an intense urge to move around’⁹³. Akathisia is now known to be a common side effect of both SSRIs and antipsychotics, and is believed to be linked to the drug’s interference with the dopamine system⁹⁴. Drug-induced akathisia can be an intolerable symptom, and unsurprisingly psychiatrists will often seek to counter the effects by introducing new medication. In a recent article in the British Journal of Psychiatry, Professor Michael Poyurovsky describes various drug treatments for antipsychotic-induced akathisia⁹⁵, including the use of benzodiazepines and antidepressants, which illustrates how patients can be given additional psychiatric drugs in an attempt to treat negative effects.

Psychiatric symptoms caused by withdrawal

Antipsychotics have a well-established withdrawal profile, which includes symptoms of anxiety, agitation, restlessness and insomnia.⁹⁶ In addition there is evidence showing that a psychotic episode can occur shortly after the discontinuation of these drugs, especially clozapine.⁹⁷

Benzodiazepine withdrawal is known to comprise an array of symptoms, some of which can be confused with the re-emergence of a pre-existing anxiety state while others are clearly unrelated. Unrelated symptoms include hypersensitivity to sensory stimuli, perceptual distortions, paraesthesiae and muscle twitching.⁹⁸ However many patients also complain of extreme dysphoria, an amalgam of anxiety, depression, nausea, malaise, and depersonalization which can easily be misdiagnosed.

Withdrawal from all classes of antidepressants can lead to a range of symptoms, including flu-like sensations, akathisia, agitation, aggression and severe cognitive impairment. SSRI and SNRI withdrawal can also lead to sensory disturbances, gastrointestinal symptoms, headaches and disequilibrium.⁹⁹

Duration of withdrawal

While there is general agreement surrounding the existence of these symptoms, most of the existing literature describes psychiatric drug withdrawal as self-limiting and typically resolving within a few weeks.¹⁰⁰ However withdrawal charities report numerous examples of clients taking one or more years to recover from withdrawal from benzodiazepines and antidepressants. According to Ian Singleton of the Bristol Tranquilliser Project: 'Most people will have symptoms once they come off these drugs for at least a year... the majority will recover in their second year. But there are some who will take several years.'¹⁰¹

A longer withdrawal period is more likely to lead to misdiagnosis, especially if it appears to be at odds with reports in the medical literature. For example, Dilsaver and Alessi write: 'A clinically stable patient for whom withdrawal of neuroleptics is indicated who becomes anxious, agitated, restless, and experiences insomnia within the first few days after discontinuing treatment with a neuroleptic is more apt to be suffering from an acute withdrawal syndrome than to be in the process of relapse.'¹⁰² This implies that a person suffering such symptoms after just a few days may in fact be experiencing relapse. However other research points to withdrawal symptoms from antipsychotic discontinuation lasting 6 to 12 weeks¹⁰³ and it is known that some patients experience tardive dyskinesia, a long-term or even permanent drug-induced syndrome¹⁰⁴.

Professor Heather Ashton, a leading expert on benzodiazepines, writes that most estimates in the literature suggest that the duration of benzodiazepine withdrawal is between 5 and 28 days. However she notes numerous cases of withdrawal symptoms continuing for much longer: 'For some chronic benzodiazepine users, withdrawal can be a long, drawn-out process. A sizeable minority, perhaps 10% to 15% develop a "post-withdrawal syndrome" which may linger for months or even years.'¹⁰⁵

According to the withdrawal charities, SSRI and SNRI antidepressants often have an even longer withdrawal syndrome than benzodiazepines. Ian Singleton of the Bristol Tranquilliser Project explains: 'Antidepressants seem to cause just as many problems as benzodiazepines... many of the symptoms are the same as benzodiazepine withdrawal... In many cases we have found that the symptoms of antidepressant withdrawal go on for even longer than benzodiazepine withdrawal.'

Dr. Stuart Shipko, a Californian psychiatrist who has published on benzodiazepine and antidepressant withdrawal, opens up the possibility that withdrawal from SSRIs may even lead to a permanent state of what he describes as 'tardive akathisia'. He writes that: 'The problems that sometimes occur when people try to stop an SSRI antidepressant are much more severe and long-lasting than the medical profession acknowledges, and there is no antidote to these problems... My clinical observation is that long lasting symptoms occur even in patients who taper very slowly, not just those who stop quickly, and that there is no guarantee that these symptoms will go away no matter how long the patient waits.'¹⁰⁶

It is clear that the lack of consensus surrounding the duration of withdrawal symptoms leads to confusion for many doctors and patients, increasing the likelihood of misdiagnosis and the addition of unnecessary medication. In addition, the extreme nature of the symptoms can lead to alternative medical explanations leading to unnecessary tests and treatments. For example, Dr. Peter Haddad describes two patients who withdrew from antidepressants and were misdiagnosed as having suffered a stroke; the symptoms were so severe that neither could walk unaided.¹⁰⁷

In another paper, Haddad describes five ways in which antidepressant discontinuation symptoms can lead to misdiagnosis and unnecessary treatment. This includes misdiagnosis as a recurrence of the underlying psychiatric illness: 'Discontinuation symptoms that follow recovery from a depressive illness and termination of antidepressant treatment may be misdiagnosed as a recurrence of depression, i.e. a

further depressive episode. This may lead to unnecessary reinstatement of the antidepressant and a more negative prognosis, with significant social implications.¹⁰⁸

Dr. Joanna Moncrieff believes that psychiatric drugs may, over time, perpetuate the very disorders they were intended to treat. She argues that 'the problems that occur after discontinuation or reduction of long-term psychiatric drug treatment may be caused by the process of drug withdrawal itself... the recurrent nature of psychiatric conditions may sometimes be iatrogenic.'¹⁰⁹

Polypharmacy

Despite relatively few studies considering the safe interaction of different psychiatric drugs, multiple drug therapy is commonplace in psychiatry. According to a paper published in 1995 in the US, patients seen by a psychiatrist were six times more likely to receive multiple psychotropic medications, as compared with those seen by a primary care doctor.¹¹⁰ A 2010 report revealed that in the US about 60% of patients with psychiatrist office visits leading to a drug prescription received at least two medications in 2005-2006, according to government survey data, up from about 43% in 1996-1997. However the authors warn: 'While some of these combinations are supported by clinical trials, many are of unproven efficacy...These trends put patients at increased risk of drug-drug interactions with uncertain gains for quality of care and clinical outcomes.'¹¹¹

In the UK withdrawal charities frequently encounter patients who have been put on multiple psychiatric medications, often in order to counter withdrawal or other negative effects. As Ian Singleton from the Bristol Tranquilliser Project says: 'It's very common for people in withdrawal to find that doctors ascribe their symptoms to other things, leading to other drugs such as antidepressants and major tranquillisers [antipsychotics] which can be extremely difficult to come off. This means that instead of withdrawal taking a year or two, you might be looking at 5 to 10 years for those people to get fully well. It's a total waste of their life.'¹¹²

There is clear evidence linking the negative and withdrawal effects of psychiatric drugs with misdiagnosis and the addition of inappropriate medication. Doctors need to be made much more aware of these effects, and more research needs to be undertaken to understand their prevalence and the true risks of psychiatric drug harm.

Psychiatric drug withdrawal can be disabling

Withdrawal from psychiatric drugs can be disabling and can cause a range of severe physical and psychological effects which often last for months and sometimes years; in some cases, withdrawal charities report, it may lead to suicide.

Withdrawal from psychiatric drugs can result in many long-term disabling effects; the severe physical and psychological symptoms can impact negatively on many aspects of a person's life, threatening relationships, careers and financial stability. Withdrawal can also be very long-lasting despite the claims of some studies which suggest a recovery period of several weeks to a few months^{113, 114}. Withdrawal charities report numerous examples of clients taking one or more years to recover. According to Ian Singleton of the Bristol Tranquilliser Project: 'Most people will have symptoms once they come off these drugs for at least a year... the majority will recover in their second year. But there are some who will take several years.'¹¹⁵

Antidepressants

Antidepressants are the most commonly prescribed psychiatric drug in the UK, with over fifty million prescriptions dispensed in England in 2012.¹¹⁶ There are treatment side effects associated with their use and a withdrawal syndrome is commonly experienced upon discontinuation. Typical antidepressant withdrawal symptoms include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal. Dizziness, electric shock-like sensations, zaps, diarrhea, headaches, muscle spasms and tremors, agitation, hallucinations, confusion, malaise, sweating and irritability are also reported.^{117, 118}

There is also evidence that antidepressant discontinuation can induce mania and hypomania. Naryan and Haddad (2010) concluded that antidepressant discontinuation hypomania/mania is a valid syndrome¹¹⁹ while Goldstein *et al* (1999) conducted similar research into the development of manic symptoms on antidepressant discontinuation in patients with bipolar disorder; the results suggest a paradoxical effect whereby antidepressant discontinuation actually induces mania.¹²⁰

An analysis of over two thousand emails sent following a BBC Panorama documentary investigating patients' problems with the SSRI paroxetine showed that reports of 'electric head, with linked whooshing sensations were the most common, distressing, disabling and distinctive feature of withdrawal'.¹²¹ And in a recent study Holguín-Lew and Bell (2013) identified cases where, after treatment with an SSRI antidepressant, patients were left with an inability to cry.⁷

Sexual dysfunction is a common effect of SSRI and SNRI antidepressants. In a 2002 study, between 36% and 43% of subjects taking these drugs experienced this symptom, and the authors conclude that 'sexual dysfunction is considerably underestimated by physicians'.¹²² More worrying are numerous reports of long-term or even permanent sexual dysfunction following withdrawal from antidepressants.¹²³

Further research is clearly needed to establish the prevalence of such post-SSRI sexual dysfunction, and to investigate the incidence of other long-lasting symptoms, as reported by various withdrawal charities and patient groups. Dr. Stuart Shipko, a Californian psychiatrist who has published on SSRI withdrawal, no longer advises patients who have been on SSRIs for more than ten years to try to stop unless they are willing to risk disabling symptoms, including a state of agitation and inner restlessness which he calls 'tardive akathisia'. He states that his 'clinical observation is that long lasting symptoms occur even in patients who taper very slowly, not just those who stop quickly, and that there is no guarantee that these symptoms will go away no matter how long the patient waits'.¹²⁴

A recent report by the OECD confirms a dramatic increase in the prescribing of antidepressants across the developed world, with estimates that as many as one in ten adults take these drugs regularly¹²⁵. Part of this increase is due to increasing numbers of long-term users, many of whom will find themselves

unable to withdraw from the drug because of intolerable symptoms, or a belief that such symptoms represent the return of an underlying condition or even a new illness (see Negative Effects Lead to More Drugs on the CEP website).

Despite hundreds of millions of patients taking antidepressants worldwide there is no research supporting the safe long-term use of these drugs while ample evidence exists of the potential for serious harm.

Benzodiazepines and z-drugs

Approximately 17 million prescriptions for benzodiazepines and z-drugs were issued in England during 2011¹²⁶ and an estimated 1-1.5 million people in the UK take these drugs regularly, despite clear guidelines stating a maximum of 2-4 weeks use¹²⁷. Withdrawal from these drugs can cause a host of disabling symptoms; these symptoms can also be experienced while taking the drug, as tolerance sets in and higher doses are required to stave off withdrawal.

Professor Heather Ashton became a leading authority on benzodiazepine withdrawal after managing a large withdrawal clinic in the 1980s. She describes a range of withdrawal symptoms, broken down into physical and psychological categories. Psychological symptoms include insomnia, nightmares, increased anxiety, panic attacks, agoraphobia, perceptual distortions, depersonalisation, derealisation, hallucinations, depression, obsessions, paranoid thoughts, rage, aggression, irritability, poor memory & concentration, intrusive memories. Physical symptoms include headache, pain/stiffness, tingling, numbness, altered sensation, fatigue, influenza-like symptoms, muscle twitches, jerks, tics, 'electric shocks', tremor, dizziness, light-headedness, poor balance, blurred/double vision, sore or dry eyes, tinnitus, hypersensitivity, gastrointestinal symptoms, constipation, pain, distension, difficulty swallowing, appetite/weight change, dry mouth, metallic taste, unusual smell, sweating, palpitations, over-breathing, urinary difficulties/menstrual difficulties, skin rashes and itching.¹²⁸

In his analysis of adverse behavioural effects of benzodiazepines, Dr. Peter Breggin also states that benzodiazepines can produce a wide variety of abnormal responses and hazardous behavioural abnormalities, including rebound anxiety and insomnia, mania and other forms of psychosis, paranoia, violence, antisocial acts, depression, and suicide. He describes how the drugs can impair cognition, especially memory, and can result in confusion.¹²⁹

It is now recognised that withdrawal symptoms for long-term users coming off benzodiazepine and z-drug can last 6 to 18 months after the last dose, and sometimes even longer¹³⁰. Withdrawal charities report numerous cases of patients taking at least three or four years to recover, and some are left with residual symptoms such as tinnitus which can persist for years beyond this timeframe. Professor Ashton describes various patients who continue to experience symptoms long after withdrawal, which she defines as a 'protracted withdrawal syndrome'. She notes her own experience with patients who complained of symptoms such tinnitus, anxiety, motor symptoms, gastrointestinal symptoms and paresthesia, which in some cases lasted at least four years. She concludes that: 'It remains possible that some protracted benzodiazepine withdrawal symptoms (including tinnitus and other neurological and psychological symptoms) could result from physicochemical neuronal damage'.¹³¹

It should be noted that there are many similarities between benzodiazepine/z-drug and antidepressant withdrawal symptoms. In a study reviewing the difference between SSRI and benzodiazepine withdrawal reactions Nielsen et al (2012) concluded that 'discontinuation symptoms were described with similar terms for benzodiazepines and SSRIs, and were very similar for 37 of 42 identified symptoms... referring to these reactions as part of a dependence syndrome in the case of benzodiazepines, but not selective serotonin re-uptake inhibitors, does not seem rational.'¹³² Withdrawal charities also report similar experiences among individuals withdrawing from either an antidepressant or a benzodiazepine, or both. According to Baylissa Frederick of Recovery Road: 'There has not been a noticeable difference in symptoms experienced. Both can be as horrific... both can be as intense, as lengthy, and with similar repercussions'.¹³³

Patient groups report several cases of individuals who have committed suicide as a result of intolerable withdrawal symptoms. In addition, two studies reviewing outcomes of benzodiazepine withdrawal included suicides among relatively small groups of subjects; in both cases withdrawal symptoms were considered as a factor.^{134, 135}

Antipsychotics

Antipsychotics have a well-established withdrawal profile, which includes symptoms of anxiety, agitation, restlessness and insomnia.¹³⁶ In addition there is evidence showing that a psychotic episode can occur shortly after the discontinuation of these drugs, especially clozapine.¹³⁷ Other studies show a range of antipsychotic withdrawal symptoms, including nausea, emesis, anorexia, diarrhea, rhinorrhea, diaphoresis, myalgia, paresthesia, anxiety, agitation, restlessness, and insomnia.¹⁷

While some research suggests that antipsychotic withdrawal only lasts a few days¹³⁸, other research points to withdrawal symptoms lasting 6 to 12 weeks¹³⁹ and it is known that some patients experience tardive dyskinesia, a long-term or even permanent drug-induced syndrome¹⁴⁰.

Other effects of withdrawal

As with other serious chronic illnesses, withdrawal can have devastating effects on a person's life beyond the physical and psychological symptoms. Dr. Joanna Moncrieff describes the broader impact of withdrawal: 'If symptoms are troubling and go on for a long time... in some cases people find that they can't get back to work, lose their jobs, they might split up with their family because they continue to be impaired by these symptoms. They will lose their confidence, be depressed as a result of withdrawal and be anxious about the future'.¹⁴¹

The disabling effects of withdrawal also adversely affect family members who, with no understanding of how to manage the complex physical and psychological symptoms, are often overwhelmed and find it difficult to provide adequate and appropriate support.

Psychiatrist Dr. Ronald Gershman writes: 'I have treated ten thousand patients for alcohol and drug problems and have detoxed approximately 1,500 patients for benzodiazepines – the detox for the benzodiazepines is one of the hardest detoxes we do. It can take an extremely long time, about half the length of time they have been addicted – the ongoing relentless withdrawals can be so incapacitating it can cause total destruction to one's life – marriages break up, businesses are lost, bankruptcy, hospitalization, and of course suicide is probably the most single serious side effect.'¹⁴²

Withdrawal from psychiatric drugs is often a devastating experience for patients and their families, and is under-recognised by doctors and the medical establishment. CEP calls for much greater recognition of this issue, and for additional research to establish its prevalence and to consider potential treatments. CEP also urges patients and doctors to use these drugs cautiously and for as short a period as possible. Withdrawal from psychiatric drugs should almost always follow a slow, structured taper, often over several months or more.

More medicating of children

Use of psychiatric drugs in children and adolescents has been rapidly expanding across the developed world. The potential long-term damage these drugs can have on developing brains has not been properly assessed. Furthermore, there is now evidence that increased use of medication within this age group may lead to worse long-term outcomes.

Recent figures suggest we are now in the midst of a global epidemic of child and adolescent psychiatric disorders. For example, it has been estimated that 1 in 10 children and young people aged between 5 and 16 have a clinically diagnosed mental health disorder.¹⁴³ Increasing rates of diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) have boosted this figure with recent estimates suggesting that around 5% of the global child population suffers from ADHD.¹⁴⁴

Figures like this are concerning because there no clear biological markers or causes that have been discovered for child and adolescent psychiatric disorders, including for ADHD. Nevertheless, child and adolescent psychiatric disorders are still being represented and treated as though they are biologically based conditions. This in turn has fuelled huge increases in the dispensing of psychiatric drugs to young people. For example, NHS prescriptions for the stimulant Methylphenidate have increased from around 420,000 in 2007 to around 657,000 in 2012,¹⁴⁵ a rise of 50% in just six years. Methylphenidate is usually given to children and adolescents to treat ADHD symptoms.

Data concerning the safety and efficacy of such drugs is far from reassuring. In 1999, a large trial tested the efficacy of Methylphenidate for children diagnosed with ADHD, with the authors concluding that drug treatment was more beneficial than behavioural treatment alone¹⁴⁶. The findings led to many organizations, including the Department of Health, recommending that such stimulant medication should be the first line of treatment for ADHD despite serious questions being asked regarding the study's methodology, the conflict of interests of its authors, the selection and recruitment process, the behavioural interventions used and the lack of attention to side effects.^{147, 148} This highly influential study followed up the participants at 24 months, 3 years and beyond and found that stimulants were no more effective in the longer term than behavioural treatment, and on some measures was less effective.^{149, 150}

Criticisms of stimulant treatment deepened in September 2005 when the Oregon Health & Science University Evidence-Based Practice Center published the findings of a comprehensive review of studies conducted on ADHD drugs. Their review concluded that evidence for the common belief that these drugs could positively affect 'academic performance, risky behaviours, social achievements, etc.' was lacking. In addition the authors stated: 'We found no evidence on the long-term safety of drugs used to treat ADHD in young children or adolescents.'¹⁵¹ This finding is consistent with other long-term studies that have shown no evidence of long-term improvement and an increased likelihood of adverse outcomes^{152, 153}. As the leading ADHD researcher Dr. William Pelham summarised, 'No drug company in its literature mentions the fact that 40 years of research says there is no long-term benefit of medications for ADHD. That is something parents need to know.'¹⁵⁴

Adverse effects of stimulants

Stimulants are known to cause an array of adverse effects, which include poor appetite, weight loss, growth suppression, insomnia, depression, irritability, confusion, mood swings, obsessive compulsive behaviors, psychosis, explosive violent behavior, personality change, lowered self-esteem, loss of creativity, disinterest, a flattening of the emotions, stomach ache, headaches, movement disorders, tachycardia, pituitary dysfunction and dizziness.¹⁵⁵

Stimulants can produce many other adverse reactions, including persistent brain dysfunction and some believe this can include potentially irreversible central nervous system damage. A well-known critic, Dr.

Breggin, has claimed: 'Enough is already known about the lack of benefit and the negative impact of stimulants to stop prescribing them for ADHD or for the control of any symptoms or behaviors in children.'¹⁵⁶ Researchers at the University of Buffalo have conducted studies that showed that Ritalin might also cause long-lasting changes in brain function. This study, conducted on rats, showed changes similar to those caused by the use of cocaine.¹⁵⁷ Furthermore, there is growing evidence that stimulant-induced biochemical changes can be irreversible, with studies showing that amphetamine and methamphetamine can cause permanent neurotransmitter system changes and cell death.¹⁵⁸

In addition, stimulants are drugs of abuse. One study followed 492 children into their late 20s and found a significant increase in cocaine and tobacco dependence amongst ADHD subjects treated with stimulants compared to ADHD controls who did not receive stimulant treatment. This study concluded that there was 'a significant difference in rates of daily smoking and tobacco dependence for those with ADHD who had used stimulant medication in childhood in contrast to controls.'¹⁵⁹

Antidepressants

Antidepressants are now widely prescribed to young people, despite evidence that seriously challenges the efficacy and safety of both the older tricyclic antidepressants and the newer selective serotonin reuptake inhibitors (SSRIs). In 2004, for example, Jureidini and colleagues reported that none of the studies on SSRI antidepressants for childhood depression have, relying on patient or parent-reported outcomes, showed significant advantage over a placebo.¹⁶⁰ A review by the FDA of all clinical trials of antidepressants in children and adolescents showed that 4% of all subjects experienced suicidal thinking or behaviour, including actual suicide attempts – twice the rate of those taking the placebo. This led to a black box label warning in the US in 2004, warning about the increased risk of suicidal ideation in the under 18 age group when taking SSRI antidepressants.¹⁶¹

In 2004 The Lancet published a meta-analysis of published and unpublished clinical trials of SSRI antidepressants on children. The study concluded that 'the published data suggest a favourable risk-benefit profile for some SSRIs; however, addition of unpublished data indicates that risks could outweigh benefits of these drugs (except fluoxetine) to treat depression in children and young people.' The authors of the study were highly critical of the practice of withholding negative clinical trial data: 'Drug sponsors who withhold trial data (or do not make full trial reports available) undermine the guideline programme, which can ultimately lead to recommendations for treatments that are ineffective, cause harm, or both.'¹⁶²

Such behaviour led Dr. Sami Timimi – a prominent UK child psychiatrist – to conclude: 'I believe that an unhealthy interdependence between pharmaceutical companies and doctors has skewed child psychiatric practice toward over diagnosis and overprescribing and has diminished our ability to use non-medication-centred and more context-rich approaches.'¹⁶³

Given concerns over the safety and efficacy of these medications as well as the behaviour within the pharmaceutical industry, the Medicines and Healthcare Products Regulatory Agency (MHRA) decided in 2003 to disapprove the use of these drugs, with the exception of Prozac (fluoxetine), in children and adolescents.¹⁶⁴ Despite this disapproval, it is still perfectly legal for doctors to prescribe SSRI antidepressants, off label, to children and adolescents.

CEP calls for three changes with respect to the medicating of children and adolescents: firstly, an objective, evidence-based approach to evaluating these drugs; secondly, better public understanding of how these medications work, and thirdly, a more evidence based approach to evaluating the risk/benefit profile for psychiatric medications given to young people including the recognition of potential long term harms.

Regulator funded by industry

The UK regulator of psychiatric drugs (the MHRA) is entirely funded by the pharmaceutical industry, and employs ex-industry professionals in key leadership positions. Such conflicts of interest could lead to lenient regulation that places commercial interests above patient protection.

The [MHRA] has been too close to the industry, a closeness underpinned by common policy objectives, agreed processes, frequent contact, consultation and interchange of staff.

(House of Commons Health Committee Report, 2004)

In September 2013 the MHRA appointed its new Chief Executive. His name is Ian Hudson, and for 12 years prior to his appointment he was an employee of the pharmaceutical company, GlaxoSmithKline. For much of his time at GlaxoSmithKline he was a director at the company. Yet when he was appointed as head of the MHRA, there were no questions raised (in parliament, in the media or elsewhere) about whether an ex-director at GlaxoSmithKline should become chief executive of the very agency responsible for regulating the products of companies like GlaxoSmithKline.

In fact, such questions are rarely raised in the places that count. This is surprising since the composition of the MHRA's current executive committee includes so many ex-industry professionals:

- Ian Hudson (Chief Executive of the MHRA), previously Head of Global Safety at GlaxoSmithKline
- Gerald Heddell (Director of the Inspection, Enforcement & Standards Division), previous posts include European Quality and Compliance Director for GlaxoSmithKline
- Stephen Inglis (Director of National Institute for Biological Standards and Control), previously Research Director of Cantab Pharmaceuticals
- John Parkinson (Director of Clinical Practice Research, Datalink), previously consultant to the pharmaceutical and wider healthcare industries

The MHRA has a conflict of interest policy, but this policy does not militate against the less obvious biases and allegiances that inevitably develop over years of working within a given sector. Such learned tendencies and dispositions to act in ways consistent with company interests can make individuals less impervious to industry lobbying. No existing conflict of interest policy, including the MHRA's, can protect against these subtle yet potent forms of influence. The only protection fit for purpose is to ensure that your regulatory team is not recruited from the very industry whose products it is supposed to regulate.

Alongside the MHRA being governed by ex-industry professionals, the costs it incurs for regulating medicines in the U.K. are, as the MHRA states, entirely 'met by fees from the pharmaceutical industry'.¹⁶⁵ In other words, the regulation of all medical drugs in the U.K. (psychiatric and otherwise) is entirely funded by the very industry whose success or failure depends upon whether its products are approved by organisations like MHRA.

The term used in academia to describe this arrangement is 'regulatory capture'. A regulatory body is 'captured' when it is financially dependent upon the industry it regulates. This arrangement makes sense to industry, as it would rather be regulated by those financially dependent upon it, than by those fully independent of its influence. The most common and obvious outcome of 'regulatory capture' is that

regulation becomes lenient, putting company interests above the interests of those regulation should serve and protect – namely, patients.

Examples of this leniency are easily found. For instance, the MHRA requires only 2 clinical trials to approve a psychiatric drug for public use, even if there exist 4, 5, 6, or more negative trials. In a practice for which there is no clear scientific justification or rationale, the MHRA simply discards the negative trials. This means, in short, that even if 10 negative trials exist, on the basis of only one or two positive trials the drug can still be approved for public use. As the MHRA stated in an email correspondence with a member of CEP in 2012:

As a general rule a minimum of two studies is required to prove the efficacy of a drug. A single study will have to demonstrate very compelling results to be considered sufficient alone to demonstrate efficacy.

Such lenient regulation is exacerbated since industry funding for the MHRA is not guaranteed. In short, regulatory bodies compete among each other to be the regulator that industry prefers, and therefore funds. As the House of Commons Health Committee reported in 2004:

[The MHRA] needs to keep a close eye on its market share of regulatory business: increasingly it competes with other European drug regulatory agencies to scrutinise drug licence applications. Like any other regulatory agency, the MHRA walks something of a tightrope, trying to strike a balance between support for the industry and effective medicines control.

An independent regulatory body would not have to walk this ‘tightrope’ by keeping its regulation industry-centered and lenient.

A method by which the MHRA protects such leniency is by avoiding full transparency. As the aforementioned Government Health Report stated:

The process by which drugs are licensed is far from transparent. There is no public access to the data presented by the pharmaceutical companies nor to the assessments undertaken by the MHRA. There is not enough involvement of patients, the public and the wider scientific community, and the Agency does not listen or communicate well...

(House of Commons Health Committee Report, 2004)

As Sir Ian Chalmers continues:

Denial of access to information held by the [MHRA] puts the interests of pharmaceutical companies ahead of those of patients and prescribers. This is particularly indefensible in the light of evidence that regulatory agencies, supposedly established to protect the public, are acquiescing in biased later publication of the information they hold.

(Sir Ian Chalmers, quoted ibid: 79)

To conclude with the words of Professor Andrew Herxheimer, Emeritus Fellow, UK Cochrane Centre, Oxford:

...when the agency was hived off from the Department of Health...the culture became confirmed that the industry is the client and the client must be looked after: quick service, good service, easy contact, etcetera - so it is a closed community in a sense

(Dr. Herxheimer, quoted ibid: 78)

CEP calls for a fully independent regulatory body; one that will only use ex-industry professionals for consultancy purposes, but won't appoint them to key leadership positions; one that is also taxpayer funded and so entirely independent of the industry payments upon which the MHRA currently depends.

Conflicts of interest

Ties between doctors and the pharmaceutical industry are particularly widespread in psychiatry. In the UK psychiatrists do not have to report to any agency or authority how much industry income they receive each year.

An open letter written by many concerned medical professionals was recently published in the British Medical Journal (Jan 2014):

Trust between patients and doctors is critical to good medical practice, and doctors are still highly trusted by the public.¹⁶⁶ But we should ensure that we deserve it. The Association of the British Pharmaceutical Industry has estimated that the drug industry pays £40m (€48m; \$65m) a year to [U.K. based] doctors for speaking fees, flights, hotels, and other travel expenses.¹⁶⁷ Yet who is being paid what is opaque. It is clear that exposure to pharmaceutical advertising adversely affects future prescribing.¹⁶⁸ There is also evidence that if doctors accept gifts from the drug industry, patients trust doctors less.¹⁶⁹ Citizens can access MPs' central register of their financial conflicts of interest,¹⁷⁰ yet patients cannot find out whether their doctor has a financial conflict of interest.¹⁷¹

The above article refers to doctors from the whole of medicine. At CEP we are predominantly interested in the links between industry and psychiatry, especially because research suggests that over the last 30 years the ties between psychiatry and industry may have become closer than in almost any other medical specialism. For instance, a recent study conducted by ProPublica, a respected Watchdog charity, has shown that half of the highest payments made by the pharmaceutical industry to the *whole* of medicine were made to doctors from a *single* specialism: psychiatry.¹⁷²

This was a study of American psychiatrists, but these payments are widespread in Britain too. This can be inferred from an inspection of the 'declarations of interest' that researchers disclose in their published research. These reveal that most British leaders in psychiatric drug research have had financial ties to industry at one point or another. Furthermore, most British and American psychiatry departments now receive income from drug companies for research and/or other activities. A recent Freedom of Information request asked eight British universities chosen at random to disclose industry funding to their psychiatry departments or psychiatric faculty. These universities included Oxford, Cambridge, Manchester, Liverpool, The Institute of Psychiatry (Kings London), University College London, Newcastle and Edinburgh.

Two of these universities declared they hadn't gathered the figures, a third declared (it turns out wrongly) that their psychiatrists had received no money, a further set of figures is outstanding, while the remaining four declared their payments:

- The Psychiatry Department at the University of Newcastle took over £5.5 million from the industry in years 2009 to 2012 (this figure was only for research funding, and does not include payments received by individual psychiatrists for consultancy work and speakers' fees – so the final figure will presumably be far more).
- The Institute of Psychiatry reported receiving £1.87 million between 2009 and 2012 (this figure does not include payments for consultancy work and speaker's fees).
- The Psychiatric Department at University of Oxford had received £687,000 from the pharmaceutical industry from 2009 to 2012 (this figure once again does not include payments received for consultancy work and speakers' fees).

- The Division of Psychiatry at The University of Edinburgh received £1.59 million in research funding the last 3 years (again, this figure does not include payments for consultancy work and speaker's fees).

None of the above universities would disclose their psychiatrist's private industry income for consultancy work, speaker's fees etc. And in many cases this was simply because the university did not request this information. As Liverpool University put it, psychiatrists 'are not required to report individual payments to the University so we don't hold any information which could be provided in response to this part of the request'.¹⁷³

Turning our attention to the diagnostic manuals, many members of the committees who put together the DSM have had strong industry ties. With respect to DSM IV (the DSM edition used in psychiatry between 1994 and 2013) a recent study by the University of Massachusetts showed that of the 170 panel members of DSM IV, a full 56% had one or more financial associations with the pharmaceutical industry.¹⁷⁴ And for the disorders for which drugs are the first-line of treatment (e.g. the mood disorders, eating disorders, psychotic disorders and anxiety disorders), an average of 88% of all DSM IV panel members had drug company financial ties. This trend has continued in the new DSM-5 (published May 2013). Of the 29 Taskforce members writing the manual, a full 21 have received honoraria, consultancy fees or funding from pharmaceutical companies, including the Chair of the Taskforce, Dr. David Kupfer, and the Vice Chair, Dr. Darrel Regier.¹⁷⁵

The Sunshine Act in the U.S. is now tackling these problems by obliging U.S. doctors to declare their pharmaceutical ties publicly. Right now in Britain, there is no equivalent; no public register of payments. There is a European initiative to change this (see¹⁷⁶) as well as the 'Who Pays this Doctor' campaign (see¹⁷⁷), but the specifics and implementation of the former are still unclear, while the latter is only a voluntary register (to which, at the time of writing, only a handful of doctors have signed up).

Until all doctors are legally obliged to lodge all payments received on a public register, there is no way of identifying those doctors with potential conflicts of interest. The same must be said for mental health organisations and charities: we have a right to know whether a mental health organization that speaks favourably about antidepressants, receives yearly donations from antidepressant manufacturers. To quote James Davies¹⁷⁸:

Until there are public websites where such payments are made fully transparent and which therefore enable the full extent of the problem to become clear, the real debates about how to reform industry ties won't even begin: should there be limits placed on what doctors receive yearly? To what extent should industry payments be donated to charity? To what extent should un-paid voluntary industry service be obligatory (for which companies then reimburse the NHS)? These are no doubt thorny issues, which warrant long and hard debate. But right now these debates are not only avoided, they aren't even being proposed in the places that count.

CEP supports full transparency in the form of an online register that documents industry payments to individuals and organisations.

Manipulation and burying of drug trial data

The majority of psychiatric drug trials are conducted and commissioned by the pharmaceutical industry or those who have extensive ties with them. This industry has a long history burying negative results, and of manipulating research to highlight positive outcomes.

In 2005 a report by the British government's Health Committee identified some of the practices by which pharmaceutical companies research and present their findings. The practices brought to the attention of the report's authors included:

...that clinical trials were not adequately designed – that they could be designed to show the new drug in the best light – and sometimes fail to indicate the true effects of a medicine on health outcomes relevant to the patient. We were informed of several high-profile cases of suppression of trial results. We also heard of selective publication strategies and ghost-writing. The suppression of negative clinical trial findings leads to a body of evidence that does not reflect the true risk/benefit profile of the medicine in question.¹⁷⁹

Today the pharmaceutical industry funds most of the clinical trials into their own products. They develop and conduct the trials, and evaluate and often manipulate the results. They are not obligated to publish the results of trials and rarely provide raw data for external review. Moreover, trials with positive outcomes are much more likely to be published, sometimes multiple times. An obvious example of this is Ely Lilly's antipsychotic, Zyprexa. Lilly conducted four clinical trials on this drug, yet turned this in to a total of 234 publications. Furthermore, none of these publications mentioned what these trials revealed: that Zyprexa increased rates of suicide or blood glucose or cholesterol levels.¹⁸⁰

Such suppression of data is endemic in the industry. For example, according to the authors of a 2008 article published in the New England Journal of Medicine, of the 74 antidepressant trials reviewed in the article, nearly half were deemed by the FDA to have either negative or questionable results. Of this half, only 3 were published accurately, the rest were either entirely buried or published in a way to convey positive outcomes.¹⁸¹

Aside from burying negative data, companies deploy other strategies to advantage their products. Many articles published in high profile journals by senior researchers with prestigious university associations are actually ghost-written by the companies. In such instances, drugs companies send the article to a well-known researcher for review and then pay for using his or her name even if the researcher has never seen a single participant and does not have access to the raw data. The percentage of ghost-written clinical trials articles has been estimated at over 50% by a House of Commons Health Committee.¹⁸²

Other questionable strategies include adopting clinical trials protocols that strongly bias the study towards positive outcomes. For example, prospective subjects are often screened to see if they would be good candidates. In one study, only about 30 of the 350 depressed patients would have qualified for a randomized controlled trial.¹⁸³ Some of the reasons for exclusion include prolonged depression, poor response to previous antidepressants and a good response to placebo. Moreover, the selected candidates are often not representative of the people who will be taking the drug and the effectiveness is likely to be less than that reported.

Clinical trials results can be further massaged by the choice of methods used to evaluate outcomes. For example, the Hamilton Depression Rating Scale (HAM-D) is often used in antidepressant clinical trials, but this scale gives more importance for a drug that causes sedation thereby reducing insomnia than it does if it causes the participant to have increased suicidal thoughts. Another analysis tactic is to remove participants from the study if they cannot tolerate the drug and must discontinue usage regardless of the

symptoms, such as suicidal thoughts. They are not counted as failures for the effectiveness of the drug and are deemed non-compliant.

Another often-criticized strategy used in clinical trials is failing to differentiate clearly between placebos and the drug effect. Since many psychiatric drugs have strong side effects, participants can usually tell and the real drug from the fake pill thereby undermining the validity of controlling for the placebo effect.¹⁸⁴ Moreover, because of their short duration, clinical trials don't allow for a long-term evaluation of a drug's effectiveness or indeed its safety.

These and other strategies were identified by the former chief editor of the British Medical Journal, Dr Richard Smith, in a paper titled *Medical Journals are an Extension of the Marketing arm of Pharmaceutical Companies*. Here he described how pharmaceutical companies have manipulated drug-trial data in ways so initially undecipherable that, as he confessed, it took 'almost a quarter of a century editing for the BMJ to wake up to what was happening'.¹⁸⁵ Here are some of the strategies Smith identified:

- Conduct a trial of your drug against a treatment known to be inferior (your drug therefore looks superior).
- Trial your drugs against too low a dose of a competitor drug (your drug looks superior).
- Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic).
- Conduct trials that are too small to show differences from competitor drugs (concealing that your drug could be inferior).
- Use multiple endpoints in the trial and select for publication those that give favourable results (thus discarding results that are unfavourable).
- Do multi-centre trials and select for publication results from centres that are favourable (again discarding negative results).
- Conduct subgroup analyses and select for publication those that are favourable.
- Present results that are most likely to impress – for example, reduction in relative rather than absolute risk.¹⁸⁶

Legal action

What further undermines trust in industry-conducted research is that many of the major manufacturers of psychiatric drugs have either been prosecuted or settled out of court for burying data. Here are just three examples¹⁸⁷.

1. The British pharmaceutical giant GlaxoSmithKline (GSK), which manufactures the antidepressant paroxetine (marketed as Seroxat in the UK and Paxil in the US). GSK conducted three trials to investigate whether this drug could reduce major depression in adolescents. But the trial results were highly inconclusive. One trial showed mixed results, another showed that Paxil/Seroxat was no more effective than a placebo, while the third suggested that the placebo might be more effective with some children. GSK published only the most positive study as evidence that the drug is effective for major depression in children. This would have gone unnoticed had not an internal company document been leaked to the Canadian Medical Association. This showed that GSK officials had actively suppressed negative results from one study because, as they said: 'It would be commercially unacceptable to include a statement that the efficacy had not been demonstrated, as this would undermine the profile of paroxetine.' Once this information came to light, a lawsuit was filed against GSK in 2004 for intentionally hiding negative findings. This was settled out of court two months later when the company paid \$2.5 million for charges of

consumer fraud – a meagre sum considering that it made \$4.97 billion in worldwide sales from the drug in 2003 alone.¹⁸⁸

2. A separate class action in 2010 revealed that the international pharmaceutical company AstraZeneca buried negative data from a study it commissioned on its antipsychotic Seroquel. This study investigated whether Seroquel worked better than an older drug when treating schizophrenia. The results showed that Seroquel was only mildly better than the older drug in improving cognitive functions such as memory and attention. But in total it was far worse than the older drug. After a year patients on Seroquel had more relapses and worse ratings on some symptom scales. They also gained on average five kilograms in weight, which put them at increased risk of diabetes. But again, AstraZeneca simply buried these negative findings, and published only the positive results, leading to the drug's approval for general use. But so many thousands of patients suffered such awful side effects that in 2010 AstraZeneca was finally forced to pay up £125 million to settle a class action out of court.¹⁸⁹
3. In 2010 an article in the British Medical Journal revealed that the drug reboxetine, marketed as Edronax by the drug giant Pfizer, was no more effective in treating major depression than a placebo sugar pill. Data on 74 per cent of the patients in Pfizer's studies of the drug were never published. If these data had been included, the evidence would have shown that the risks of taking the drug far exceeded the benefits.¹⁹⁰ Yet reboxetine has been approved for marketing in many European countries (for example, the UK and Germany) since 1997, and is still being taken by thousands of people in the UK today.

Long-term use vs short-term trials

There is very little data on the long-term effectiveness of the drugs commonly prescribed by psychiatrists. However, the data that is now emerging does not favour long-term use. (See Worse Long-term Outcomes at cepuk.org).

This is not surprising since clinical trials usually last only a few weeks or months, while many patients take psychiatric drugs for years or even decades. The effects of a drug over the short term can be very different to the cumulative effect of taking the same drug for years, and the only means of determining whether a drug is safe for long-term use is to commission research into cohorts of patients who have taken the drug long-term. For some psychiatric drugs such as SSRIs – despite the fact that each year hundreds of millions of prescriptions are given out worldwide – this work has never been done, and it is reasonable to conclude that long-term users of many modern psychiatric drugs are part of an ongoing experiment.

There are numerous examples in medical history of drugs which were initially believed to be safe and which are subsequently revealed to have caused harm. For example, benzodiazepines were touted as an entirely safe replacement for barbiturates, and millions of people took the drugs regularly during the 60s and 70s. Despite evidence of physical dependence and withdrawal symptoms appearing in the early 1970s it was not until the 1988 that UK Committee on Safety of Medicines first insisted that they should be used for a maximum of two to four weeks only to minimize the risk of addiction.¹⁹¹ Today, withdrawal charities report numerous cases of people experiencing similar lasting negative withdrawal effects after stopping antidepressants, and yet these drugs continue to be prescribed for long-term use without firm evidence that such long-term use is in fact safe.

The multiple failings of the current clinical trial system recently led Marcia Angell to conclude: 'It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine.'¹⁹²



CEP believes that the current clinical trial system is broken, and that conflicts of interest and the manipulation of trial data have led to significant patient harm. In order to rebuild public trust, trials need to operate without any industry influence, overseen by independent academic institutions.

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