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"Jagged Little Pills. Antidepressants, effective medicines or palliative narcotics ?"

In 1991 the United Kingdoms national health service spent a total of £54 million sterling on psychopharmacological antidepressant drugs. By 2002 this figure had risen to over £381 million annually, the vast majority of which (£320 million) spent on SSRIs (Medawar, 1998), so called second generation antidepressants, which selectively inhibit reuptake of the neurotransmitter Serotonin (5-HT). These drugs were attractive because initial research findings promised fewer side effects (Wenicke, 1985) and similar efficacy (Cohn & Wilcox, 1985) to previous generations of antidepressants, such as Monoamine Oxidase Inhibitors (MAOIs) and Tricyclics (TCAs). Additionally they had as support for their adoption a growing multitude of newly defined psychological illnesses, many of which included depression as a symptom. By the DSM-IV-TR, the fourth revision of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, this number had grown to over 300 (Medawar, 1998). New controls introduced on the prescription of habit forming sedatives such as barbiturates, and tranquillisers like Diazapam (UN, 1967), which had been widely used to control the US's 'epidemic' of anxiety in the 1950s and 60s, also pushed their adoption. Finally an enormous and highly focused promotional effort by the pharmacological industry on both the public and psychiatrists and doctors in a position to prescribe their newly patented and marketed medications (Rosenthal, Berndt, Donohue, Frank, Epstein, 2002), describing antidepressants as a treatment for a neurochemical imbalance ('Depression is not fully understood, but a growing amount of evidence supports the view that people with depression have an imbalance of the brains neurotransmitters' (Eli Lilly, 2003)) helped ensure that that SSRIs would become the predominant 'front line' treatment for depression in the US, and internationally (Goldberg, Privett, Ustun, Simon, Linden, 1998).

In the United states SSRIs are considered so safe and effective they have been prescribed to children as young as 3, for disorders such as severe shyness (described in the DSM-IV-TR as 'Selective Mutism') (Dotinga, 2004), and a government funded task force has recommended screening all adults attending a health professional (for any reason), for depression (Cohen & Holler, 2003).

The widespread prescription and rapid growth in popularity of SSRIs raises some important questions. Is a chemical approach to the treatment of depression, and are

SSRIs in particular, warranted by their efficacy and safety ? Is depression in fact caused by a neurochemical imbalance (such as a 5-HT deficit), or is such an imbalance, assuming it exists, an effect of depression ? And ultimately do SSRIs provide the best chance of long term remission from depression, or simply a palliative, and potentially addicting treatment ?

The discussion of the ultimate causes of depression is intimately related to the issue of the application of the medical model, and more specifically the pharmacological model, to psychopathology and mental disorder.

Depression has been observed throughout recorded history, and has been classified medically since Hippocrates defined melancholia as an excess of black bile twenty four centuries ago.

Since then, increasingly advanced medical models, whilst useful in the classification of psychological disorders, and the treatment of somatically originated symptoms and conditions, have not necessarily been scientific, nor have they inevitably resulted in the increasing efficacy of treatment.

In describing psychopharmacology as potentially unscientific, I refer to the fact that it does not inevitably proceed from the induction of theory through the collection of facts to the deduction and testing of hypothesis by experiment. The development of drugs to treat psychological disorder has often taken a haphazard approach, with drugs originally created and marketed for one use, coming to be utilized for another, for which they appear effective, rather than being purposefully designed or discovered through an understanding of the underlying biochemistry of a disorder. For example, the first MAOI Iproniazid was developed as a treatment for tuberculosis, and discovered in clinical use to have a euphoric/antidepressant effect (Perrine, 1996); similarly, the sedating effects of Lithium (currently used in the control of bipolar disorder) were discovered accidentally (Liverman, 2004).

The development of drugs in such a trial and error manner, and their application without a thorough understanding of their mechanism of operation, can lead to treatment regimes more useful for the control of the mentally ill, than the cure of their underlying disorders; and can create a potential for syndromes to emerge which are related to the unintended effects of the underlying operation of the drug. An example is the multitudinous side effects of Neuroleptics, used for decades in the control of psychosis, and in particular schizophrenia. Long term exposure to these drugs left

patients with numerous chronic neurological conditions, such as Neuroleptic-Induced Deficit Syndrome (Lewander, 1994), Tardive Dyskinesia (Glazer, 2000), and Pisa Syndrome (Suzaki, & Matsuzaka, 2002); and while they were successful in reducing the positive symptomology of schizophrenia (such as hallucinations and delusions), they increased the severity of negative symptoms, which by their nature are not as troublesome from the perspective of the control of patients (Whitaker, 2001).

Numerous theories have arisen from the field of scientific psychology to account for the prolonged irrational sadness of men, and it would appear obvious that it is a disorder as much of circumstance as biology, yet this is a conclusion requiring the support of evidence.

Psychological explanations of depression have ranged from behaviouralist conceptions of extinction due to lack of reinforcement, to cognitive models of learned helplessness or negative self schemata (Alloy, Jacobson, Acocello, 1998), and theories from the emerging field of evolutionary psychology focusing on group dominance (Sapolsky & Share, 1994). A detailed examination of each of these paradigms, whilst evidencing the social causation of depression, would still leave unaddressed the somatogenic bias inherent in the study and treatment of depression as an entirely biological process.

Advances in genetics, evolutionary psychology, and neuroscience have led to a questioning of such a presumed nature nurture dichotomy, and an acceptance of the role of genetic diathesis, in combination with dynamic environmentally dependant neurological development, in the formation of behaviour (Davison, Neale, Kring, 2004); leaving room for social and environmental explanations of depression, which attempt to inform rather than substitute for biological explanations. Studies of monozygotic twins, for example, have indicated that individuals who share a genotype do not necessarily have an equal likelihood of developing depression; leading to the conclusion that psychosocial experiences are also an important factor (Brown, 1996).

The investigation of 5-HT as a causal factor in depression, dates back to the study of the action of MAOI's, which appeared to reduce depression by inhibiting the effects of various monoamines such as Serotonin, leading to the development of the Monoamine hypothesis. This suggested that monoamines deficits (and more

specifically 5-ht deficits) were the causal factors in the development of depression (Hall, 1998)

This explanation failed to address questions such as why antidepressants are effective in treating disorders like obsessive-compulsive disorder, or why drugs which enhance serotonergic transmission, are not necessarily effective antidepressants (Hirchfeld, 2000). Additionally some of the indirect evidence which led to the formation of the Monoamine hypothesis, such as the induction of depression by substances which produce a monoamine deficit, have since been challenged (Baumeister, Hawkins, Uzelac, 2003).

The difficulty in testing the monoamine hypothesis or any other hypothesis accounting for depression in terms of levels of a given neurotransmitter, or group of neurotransmitters, partly lies in our current inability to accurately measure neurotransmitter activity in vivo. While advances in brain scanning such as fMRI allow us to record changes in localised brain temperature, blood flow and activation in real time, they do not provide a picture of the active neurochemistry of the brain. To infer this we are forced to use indirect methods such as (in animal subjects) brain slice, post mortem neurotransmitter measurements, and measures of neurotransmitters in spinal fluid (Martin, 1997). All of these methods have limitations on their usefulness, for example measuring the levels of neurotransmitters in spinal fluid does not give a direct indication of their levels in the brain, as they carry out additional functions in other areas of the body (e.g.: serotonin is used to help regulate the functioning of the intestines).

Even if the accurate measurement of neurotransmitters in the functioning organism were practical, without detailed information regarding the location and density of receptors for a given neurotransmitter, it would be of limited use; as a decrease in synaptic receptors is functionally equivalent to a deficit in the neurotransmitter which bonds to those receptors.

More recently a number of alternatives to the Monoamine hypothesis have emerged, taking into account recent advances in neuroscience. Hindmarch, 2001, suggests that depression may be an effect of hippocampal neuroplasticacy in response to stress. Alternatively researchers who have blocked neurogenisis in experimental animals have demonstrated that this inactivates antidepressants, suggesting that depression

may be related to the inadequate growth of new neurons (Vogel, 2003). Both of these hypotheses present a synthesis of environmental and neurobiological factors in the proximate causation of depression, which seems more plausible in the light of empirical experience than a solely biological explanation such as the Monoamine hypothesis.

Our lack of understanding of the functioning behind the efficacy of antidepressants begs the question, how well do they work ? Studies seem to indicate that no one SSRI works better than any other (Simon, 2001) and SSRIs do not necessarily work any better, or even as well as TCAs (Roose, Glassman, Attia, 1994). Studies comparing SSRIs like Fluoxetine directly with behavioural or cognitive therapy are difficult to come by, however earlier studies comparing TCAs with cognitive therapy alone or to combination cognitive / psychopharmacological treatments, found combination and cognitive therapy to be superior (Blackburn, 1981). This is not to say that in some cases antidepressants may not be the most successful therapeutic intervention (Byrne, & Stern, 1981), but it does question their use as the default treatment for depression. One factor making the study of the effects of antidepressants more difficult, are the significant and growing numbers of people who recover spontaneously as part of placebo groups during antidepressant drug trials (Walsh, Seidman, Sysko, 2002). This ties into the results of studies from the 1960's, indicating that a large number of patients suffering from depression would spontaneously recover (Cole, 1964). This number is so large, over fifty percent in some studies (Baldwin, 2003), that it adds further weight to the argument against prescription of antidepressants in all but the most severe cases of depression.

Antidepressants (such as SSRIs) are significantly cheaper than psychotherapy, however all have significant side effects, for example sexual dysfunction, gastrointestinal complaints and insomnia, and may in some cases lead to withdrawal symptoms (Shipko, 2002) (Couplan, Bell, Potokar, 1996). Whilst withdrawal effects are reminiscent of the cravings induced by addiction, the currently accepted DSM criteria for drug dependence does not include physical dependence, opting instead for a check list of negative impacts on social functioning (AMA, 2000).

SSRIs such as Fluoxetine (Prozac), are no longer being marketed solely as a cure for depression, as the market for antidepressants has become saturated, growing to over $11 billion a year (Jarvis, 2000), and patents for leading SSRIs such as Prozac have expired in Europe and the US, pharmaceutical companies have begun to market them for other purposes (such as PTSD, OCD, 'Social Anxiety Disorder' and Panic Disorder) (Pfizer, 2003), and for longer periods of time (Eli Lilly, 2003). Additionally a new generation of drugs based on dual serotonin-norepinephrine reuptake inhibitors (SNRIs) (Maubach. Rupniak, Kramer, 1999) and 'atypical' substance P antagonists (Stahl, 1999) are poised to launch new generations of pharmacological antidepressants.

Still the question remains. Are these drugs truly treating the root causes of depression, or are they more akin to narcotic mood enhancers ? No amount of round smiling pills (visible on several pages of the Pfizer Zolft website) can ease disquiet at the notions these drugs are being both prescribed for conditions which would better be treated either by therapy alone or combination therapy and medication, and that they may be being prescribed (as in the cases of 'Selective Mutism', and 'Social Anxiety Disorder') where no real disorder exists.
Such ease of prescription is based on the central assumption of the safety of these drugs, ignoring the potential for side effects, withdrawal symptoms, and the long term effects of chronic prescription, about which we can only guess.

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