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analysis

The drugs don't work for everyone

Doubts about the efficacy of antidepressants renew debates over the medicalization of common distress

In February this year, Irving Kirsch from the Department of Psychology at the University of Hull, UK, published a study that came as a crude wake-up call for millions of patients taking medication to combat depression. The report examined a large set of clinical trials data, including unpublished findings. These data had been submitted to the US Food and Drug Administration (FDA; Rockville, MD, USA) in order to gain approval for the most commonly prescribed selective serotonin re-uptake inhibitors (SSRIs) for the treatment of depression: fluoxetine (Prozac; Eli Lilly, Indianapolis, IN, USA), paroxetine (Seroxat; GlaxoSmithKline, Brentford, UK), venlafaxine (Effexor; Wyeth, Madison, NJ, USA) and nefazodone (Serzone; Bristol-Myers Squibb, New York, NY, USA). A comparison between patients who took the drugs and those who took placebo pills revealed that the mean difference between the two groups was below the level of clinical significance along the continuum of depressed states. With the exception of the most severely affected patients, the drugs were no better than the placebos in treating mild-to-moderate depression (Kirsch *et al*, 2008).

The study received wide attention in the media, which prompted comments such as the following in *The Guardian*: "For 12 years I've stayed on the drug [Prozac] […] and now I'm reading that it doesn't work anyway unless you've got severe depression […] Perhaps the truth is that Prozac doesn't work for people who are not clinically depressed (why should it?) and lots of people who are not clinically depressed are prescribed it by doctors" (Leader, 2008).

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Now, the pertinent question for millions of people is do antidepressants work and, if so, for what severity of depression are they effective? Or, to put it another way, are placebo pills as effective as antidepressants at treating the most severe cases of depression? However one interprets the study—and it certainly triggered a cascade of reactions among experts in the field—it is not an encouraging report, both for the drug manufacturers and for the millions of people who have been taking these drugs, believing that they improve their well-being.

Since their launch in the late 1980s, SSRIs have been an escalating success for the pharmaceutical industry. Some 40 million people have taken Prozac alone, earning tens of billions of dollars for Eli Lilly, its manufacturer. By the start of this century, Prozac had become a household word—the epitome of the modern pharmacological remedy—with millions of annual prescriptions, as well as having cult novels, films and memoirs based on it. In a relatively short time, Prozac and its sister medications have covered a huge market of patients who are apparently in need of chemical treatment and whose numbers have been increasing year on year. Even the World Health Organization (WHO; Geneva, Switzerland) has warned about a global epidemic of depression and has predicted that this condition will be second only to heart disease as the most important cause of disability by 2020 (WHO, 2008).

Yet, the question remains as to whether there is really a trend of increasing depression, or whether the increasing numbers of diagnoses of depression—and the ensuing prescriptions of drugs to treat it—merely reflect two concurrent phenomena: the medicalization of distress, and a growing view that depression is primarily a 'neurochemical' disorder that can be corrected with a simple drug.

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In fact, depression is a relatively loose term that we use to describe feelings of distress, helplessness, low mood and fatigue, and the loss of hope, energy or optimism when coping with obstacles and challenges. From an evolutionary perspective, depression might be a behaviour that protects us from following unobtainable goals and ignoring our true needs, and might help us to bring genuine needs into sharper focus (Nesse, 1999). In other words, feelings of helplessness might turn out to be our best strategy for coping with or avoiding stressful circumstances over which we have little influence.

Modern molecular research has also been unable to resolve the question of whether depression is a disease. Various reports on the discovery of 'depression genes', which confer susceptibility to the condition under demanding and adverse environments, highlight the diversity in the population with regard to how individuals respond to adversity and stress (Caspi *et al*, 2003; Lesch, 2007). The fact that these genes have not been lost during human evolution also means that they might carry alternative, advantageous properties.

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The enormously increased prevalence of reported depression in the world does not reflect marked genetic shifts over the past 50 years or changes in the strategies that individuals use to face life. Similarly, it does not represent an intensification of the hardships that we are bound to confront.

Rather, it is more likely that the apparent epidemic of depression reflects a changing attitude towards behaviours that we consider to be problematic or undesirable—and therefore worthy of medical attention and intervention. The confusion of ordinary distress with clinical depression is part of a larger trend of medicalizing behaviours, which portrays difficult aspects of everyday life as serious illnesses (Conrad, 2007). Indeed, the number of conditions regarded as mental illnesses and the number of affected individuals have grown considerably over the past few decades (Lenzenweger *et al*, 2007). From this perspective, it is not just depression that we seek to medicalize. The rapidly growing number of diagnoses of attention deficit disorder (ADD), and attention deficit and hyperactivity disorder (ADHD) in children and adolescents—and the number of prescriptions to treat these disorders—raise similar questions of whether we are witnessing a real epidemic, are trying to label 'normal' disruptive behaviours as medical conditions, or are simply acknowledging that certain behaviours might have a medical cause.

An increased awareness of symptoms and behaviours—and their diagnosis as distinct pathologies—can occur suddenly as societies somehow become less tolerant of these conditions. They might become congruent with 'styles' of disorders that align with cultural and professional norms in a particular context, period or society. Contemporary Western societies, for example, value behaviours such as self-sufficiency, productivity, initiative and individual responsibility, and have become less tolerant of disruptive and mild depressive states, which, in turn, has transformed the expectations that individuals have of themselves and of others. The continuous modern incitement to action, self-realization and assertiveness functions as a norm against which differences or deviations, such as lack of energy, low mood or resignation, and those individuals who display them, are judged to be pathological (Rose, 2003).

This modern drive towards creating disease categories on the one hand and towards conformity on the other hand operates at various levels. As the quote from the article in *The Guardian* reminds us, patients who are not clinically depressed are still prescribed antidepressants by their doctors. This shows that the medical profession, and its mental health-care ancillaries, have a great deal of authority when it comes to making societal problems the domain of medicine, and contribute to the proliferation of the treatment of mental disorders with medication. In any case, the medicalization of distress—and its treatment with drugs—has served the financial interests of the drug companies.

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When it was first published in 1952, the *Diagnostic and Statistical Manual* (DSM) of the American Psychiatric Association (APA; Arlington, VA, USA)—the handbook for mental-health professionals that lists categories of mental disorders and the criteria used for diagnosing them—listed just over 100 items (APA, 1952). The subsequent second edition in 1968 included 180 mental disorders, and the third edition in 1980 contained 292 mental disorders in its revised form. The current fourth edition, which appeared in 1994 and was updated in 2000, now lists almost 400 disorders, including 'narcissistic personality disorder' and 'body dysmorphic disorder' (APA, 2000). A fifth edition is in preparation and is expected to appear by 2012. So far each edition has unearthed more disorders than the last and, in a little less than 50 years, the total number of psychological maladies that seem to plague the general population has increased fourfold. Human nature—at the level of basic brain biology—cannot have changed so much and to such a large extent in the short time between the publication of the first and the current editions of the DSM. It seems far more likely that the authors of each subsequent edition were looking for a system that allowed reliable diagnosis and that could be inclusive, rather than exclusive,

of the many aspects of human existence. In other words, we have simply become more aware of our own myriad psychological functions and disorders.

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In order for a correct diagnosis of depression to be made, a patient must satisfy a certain number of criteria from among those listed in the appropriate section of the DSM. Some drug companies run advertisements that invite consumers to conduct self-diagnosis by using reprinted DSM checklists. Of course, in such an advertisement, the company also offers a 'cure' in the form of the marketed pills. However, depression is not a black-and-white issue and cannot be diagnosed by simply counting the number of 'yes' or 'no' answers to a checklist. As depression does not show up clearly on a brain scan and cannot be detected by a blood test, its diagnosis relies largely on the opinion of a doctor—based on the account given by a patient of his or her life. Yet, a patient interview or a questionnaire certainly cannot reflect the full experience and circumstances of an individual, and so any treatment should be tailored not only to the diagnosis, but also to the individual who is being diagnosed.

It is not only practitioners who medicalize distress and therefore drive up the sales of antidepressants or other drugs to treat conditions like ADHD. Advertisements from pharmaceutical companies also contribute to this trend through the ways in which they describe diseases and the effects of psychotropic drugs (Moynihan & Cassels, 2005). This trend was already apparent throughout the 1950s and the 1970s, when 'minor tranquillisers' were commercialized and widely disseminated. The pharmaceutical industry operated a practice of 'mystification' through which it reclassified human and personal problems as conditions worthy of medical attention (Lennard *et al*, 1970). It was "redefining as medical problems a wide range of human behaviours which, in the past, [had] been viewed as falling within the bounds of the national trials and tribulations of human existence" (Lennard *et al*, 1970). The press gave these early psychotropic medications catchy names that provided readers and potential consumers with an idea of what to expect from them, such as 'peace of mind drugs', 'aspirin for the soul', 'happiness pills' and even 'Turkish bath in a tablet'. The advertisements for these minor tranquillisers portrayed images of individuals who seemed to need the drugs to overcome everyday hurdles and difficulties in social or interpersonal contexts—although with little reference to the mechanism of how the drugs worked (Smith, 1985).

Today, most direct-to-consumer advertisements of SSRIs offer similar solutions, but also explicitly emphasize the biochemistry of the drugs. Newspaper and magazine advertisements and television commercials usually explain the mechanism of action of a drug by claiming that depression results from a lack of serotonin in the brain and that the drug will correct this chemical imbalance by inhibiting the neuronal re-uptake of serotonin. So far, there has been no proof that lower levels of neurotransmitters cause mental disorders, and ongoing work to resolve this question remains contradictory. Yet, pharmaceutical companies invoke the simplistic equation that 'low serotonin levels equal depression' to explain an unresolved and complex scientific question to a lay, non-expert audience (Lacasse & Leo, 2005). In fact, there is evidence that an excess of serotonin, rather than a deficit, is responsible for the manifestation of depressive behaviours (Lesch, 2007; Carola *et al*, 2007).

Furthermore, there are numerous studies that cast doubt on the efficacy of SSRIs, not just the most recent paper by Kirsch *et al* (2008). Although these studies could, in principle, dismantle the myth propagated by advertisements—and diminish the promise of relief and improvement—it is unlikely that they will have a major impact. Even this latest report—which was published in an open-access journal and is therefore more readily accessible to the lay user—might not decrease anti-depressant sales markedly or for a long time. The hope that patients invest in the efficacy of these drugs will not be diminished easily and, paradoxically, the drug companies might even gain an advantage from negative results. The uncertainty and ambiguity surrounding the mechanistic action and clinical efficacy of SSRIs is useful to drug manufacturers: such complex scientific uncertainty can be harnessed to propagate a particular image of a product and its further scientific investigation (McGoey, 2007, 2008).

The Kirsch report certainly adds fuel to the fire in the controversy over appropriate psychopharmacological intervention for patients with troublesome symptoms, and the use of psychoactive drugs to treat '*la condition humaine*'—that is, the challenges of daily living. It is therefore not only the pharmaceutical companies and their marketing departments that use the uncertain science to their advantage. More generally, the failure of the medical community to distinguish correctly between contextual or environmentally elicited disturbances, normal responses to stress or hardship, and dysfunctional states that persist beyond the stressor, sustains the confusion and leads to the over-diagnosis of mental illness and the prescription of psychopharmacological drugs.

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The 'Prozac era' is unlikely to come to an end as long as the modern obsession with 'depression' continues. In turn, a balanced view of depression will not be achieved until we gain a clearer appreciation of the

socio-economic, familial and cultural reasons for unhappiness, resist disease fashions and set a much higher threshold for diagnosing an authentic pathology.

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