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Editorial: What is depression?

'Depression is a common, debilitating, and potentially lethal disorder.' This is a standard opening to many a scientific paper on depression. And it is often followed by some very grim statistics. Over 300 million people in the world are estimated to live with depression, and the disorder is ranked by WHO as the single largest contributor to global disability. There is also evidence that depression has increased over the last decade (WHO, 2012, 2014). Most worryingly, adolescents with major depressive disorder are up to 30 times more likely to commit suicide.

Yet, what exactly is depression? Do all 300 million depressed people in the world suffer from the same thing, with the same aetiology? Is depression one disorder that comes in different shades of severity or is it best thought of as a heterogeneous mix of problems that we have given one common name to? And, more practically, should we be treating all depression in similar ways?

Surprisingly for such a public health menace, there are very few answers to these fairly simple questions. Below are some reasons for these difficulties.

Definitions: Psychiatrists love arguing about them. Many point out the shortcomings of classification systems such as the ICD and the DSM. For some it may be the lack of nuance in our description of depression – those subtleties picked up by skilled early 20th century clinicians but forgotten since – that causes our problems. Others would argue that our biggest problem is the reification of diagnostic criteria, meant to be an index of something, rather than the thing itself (Kendler, 2016). These people would also point out that quibbling too much about definitions is unhelpful and that these should be flexible enough so as not to constrain discovery.

The measurement of depression: This is another potential stumbling block. Going by the DSM-reliability field trials, it would appear that even two experienced practitioners would have a hard time agreeing on what depression is (Regier et al., 2013). The coefficient κ, a statistic of agreement between raters, was in the questionable range for adult (0.25) and child/adolescent patients (0.28). This compares poorly to the very good reliabilities of PTSD, ADHD and ASD. For youth with mixed anxiety-depressive disorder, the problem clinicians very commonly encounter in clinics, the reliabilities were even worse. What accounts for these worrying statistics? Some say that it is the episodic nature of depression that makes capturing it so difficult. Yet, bipolar disorder is also episodic, but its reliability scores were better.

Boundaries to normality: This is a related issue. The worry about psychiatrists overpathologizing stretches beyond the critical psychiatry movement. An English friend wrote to me, lamenting the loss of the 'bulldog' mentality that saw Britain through the horrors of WWII – partly because too much normative human suffering is now called depression. In talking to Japanese colleagues at a recent conference, they thought Western influences on their culture account for increases in the reported rates of depression – either for good or ill – so it is also the professionals who worry about boundaries. The placebo response rate in youth depression trials is staggeringly high and correlates inversely with the number of sites involved in the trial and depression severity (Bridge, Birmaher, Iyengar, Barbe, & Brent, 2009; Walkup, 2017). One obvious interpretation is that the boundaries of depression have been too elastic in some of these studies allowing cases that were highly likely to recover spontaneously.

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Situation-bound changes: Sometimes referred to as contextuality (although it has nothing to do with a text), this phenomenon befuddles clinicians. Anyone who has worked on a psychiatric ward is familiar with the following scenario. An adolescent is admitted with long-lasting, incapacitating and treatment-resistant depression. Yet, once admitted, very little depression is evident. Or, in outpatients, the young person whose depression lifts at the summer school break, only to return with a vengeance in the early autumn. For some, observing such situation-bound changes is only evidence that the main problem of depression is societal expectations, rather than a problem of 'biology'. While this thesis is problematic (after all, why are some people but not others sensitive to their environment?), the problem remains that neither our nosology nor our current measurement accommodate the contingent presentations of depression.

Subgroups: An obvious remedy to the above problems would be to come up with different subtypes of depression. Such attempts stretch back to Burton's descriptions of melancholia and include distinctions made by venerable figures in psychiatry, such as Kurt Schneider (Schneider, 1920), who introduced the concept of reactive depression. However, the value of such attempts has been doubted ever since Sir Aubrey Lewis posited a continuum rather than

distinct subtypes within depression. But he also pointed out that 'It is probably true that in some depressions the hereditary factor vastly outweighs the environmental, and that in others the reverse is the case, but to detect such cases we have only dubious means. . .' (Shorter, 2007). Perhaps, the time is ripe to take a more scientific approach to this old problem. Newer data suggest that symptoms related to reward and activity or motivation may have different underpinnings (Pan et al., 2017; Stringaris et al., 2015) and outcomes to the rest of the symptoms and similar findings suggest that the direction of appetite changes may be a good indicator of another distinctive underlying pathophysiology (Simmons et al., 2016). Is it too early to start to ask whether such biological observations can guide clinical decision-making?

Should we then get rid of the term depression altogether? Be careful what you wish for. Those who urge us to free ourselves from the shackles of our current nosology, have little to say about what it should be replaced with. Even if 'depression' were a catch-all term for psychological distress of different origins and degrees of severity, in the absence of adequate categories or dimensions to replace it, scraping the term could lead to vast confusion among clinicians and patients. Also, we must remember that depression is not the only, more-or-less imperfect, category in medicine. Haematology was not stifled in its progress because of the vastly overinclusive category of leukaemias. Through hard work and patience, there are now many subtypes of leukaemias, all validated by genetic and other markers.

Researchers can, and arguably must, treat the depression category as a postulate that is to be pitted, in a systematic way, against alternative formulations. This might mean being open to the fact that both its content may prove heterogeneous, and that its boundaries may need to shift. Advances in neuroimaging analysis show good promise for subtyping in adults (Drysdale et al., 2017). Developmentally sensitive study that take into account the environment are also gaining momentum (Luby, Belden, Harms, Tillman, & Barch, 2016). The other approach is to exploit the effects of treatment. Ketamine is an obvious means of testing mechanisms (and by extension nosological boundaries). Its strong effects do not seem restricted to the current boundaries of depression and may be related to modulation of hedonic systems more generally. Similarly, neuromodulation using transcranial magnetic stimulation (TMS) can be used to probe brain networks that will help parse heterogeneity.

Articles in this issue of JCPP demonstrate how to take such research further. The study by Van Assche et al. (p. 1301–1309) takes the family environment into account by showing how GABAergic genes (GABRR1 or GABRR2) interact with parenting styles to predict depression. The methodological rigour of the study (with a discovery and replication sample) is a great example of how to parse heterogeneity within depression.

The study by Odgers and Russell (p. 1310–1318) on the other hand, uses ecological monitoring assessment (EMA) to study how and when environmental effects elicit symptoms of disordered mood. Importantly, the study goes beyond the testing of depression to incorporate related feelings of anger and irritability. This 'in the moment' reporting adds an important layer of information complementary to the typical questionnaire report. It also lends itself to sophisticated time series analysis. The methodology is not widely employed clinically yet, but could prove very useful, particularly when trying to understand what the authors call 'behavioural reactivity' to environmental events.

Finally, the study by Glenn et al. (p. 1319–1329) focuses a recently postulated cognitive mechanism: The Death Implicit Association Test (Death IAT) where reaction times to computer presentations of word pairings such as 'death', 'me' or 'not me' are used to estimate the association between the Self and Death. The strength of the study is methodological: a novel, nonquestionnaire way of identifying people at risk for suicide. The paradigm might be extendable to other cognitions and prove to be an alternative way of identifying dimensions that cut across current psychopathology.

What *is* depression, then? The 'is' may be the problem here. A tiny word that creates huge expectations of some hidden, yet well-formed, essence out there that is waiting to be discovered. In fact depression is for now, and it is to be understood as a term that helps summarize a set of phenomena. Depression, as a term, may one day be replaced with something more helpful. It is research like that presented in this issue that will make such progress possible.

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