Heterogeneity in the prognosis of major depression: from the common cold to a highly debilitating and recurrent illness

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Two different and seemingly competing views on the diagnosis of major depressive disorder (MDD) exist. The first is that the diagnosis conflates adaptive sadness reactions with pathological states of depressed mood and that MDD is overdiagnosed and overtreated. The second is that MDD is an underdiagnosed and undertreated disorder, and one that is best characterised by a severe, chronic, recurrent or treatment-resistant course. Existing research suggests that both views are valid and merit being integrated. Anywhere from 30 to 50% of individuals will meet criteria for MDD at some point in their life. About half of these episodes are of brief duration and unlikely to recur. However, a remaining half is either chronic or recurrent. Data on the outpatient diagnosis of depression support the view that depression is simultaneously underdiagnosed and undertreated as well as overdiagnosed and overtreated. About one-third of the patients who meet criteria for MDD and receive placebos experience clinically significant and long-lasting improvement. Many other patients, however, are unresponsive to one or multiple active treatments. Thus, the diagnosis of MDD likely applies to individuals who are experiencing either normal periods of sadness or single-episode afflictions that are mild, unlikely to recur, and are placebo responsive, as well as to individuals with more severe clinical profiles. More research is needed that can help ascertain what contextual or biopsychological variables help distinguish between individuals who may be experiencing adaptive states of negative affect and those who experience severe, chronic, recurrent or treatment-resistant depressions.

Depressive disorders are currently estimated to be the 11th leading cause of disability worldwide (Murray *et al.* 2013). One of most commonly cited estimates of the prevalence of major depressive disorder (MDD) is the 16.2% figure reported by Kessler *et al.* (2003). Taken at face value, this estimate is alarming. In effect, it has been met with some skepticism as it suggests a very high prevalence of MDD (Parker, 2007*a*). However, Angst *et al.* (2015) recently published data that suggest that this may be a conservative estimate. These researchers published data from a 30-year prospective study in which individuals were interviewed at least seven different times. In that sample, 32.5% of individuals met criteria for MDD at some point during the assessment period. Their findings suggest that the prevalence of MDD is underestimated by epidemiology studies that rely on retrospective assessment of lifetime disorder status. As noted by the authors,

such a high cumulative lifetime prevalence from prospective assessments of MDD is not an empirical anomaly. For example, using data from a small sample of Australian teachers, Wilhelm *et al.* (2006) reported a 42% cumulative lifetime prevalence of MDD over a 25-year period (Wilhelm *et al.* 2006). In the Dunedin Multidisciplinary Health and Development Study in New Zealand, about 40% of the sample met criteria for MDD at some point in their life (Moffitt *et al.* 2010). Similar findings emerged from the Oregon Adolescent Depression Project in the United States (USA). Half of that sample (51%) met criteria for MDD at some point before the age of 30 (Rohde *et al.* 2013). Thus, if there should be any skepticism regarding the estimates of Kessler *et al.* (2003), it is that they appear to be underestimates! Because even the prospective studies only report prevalence data up to the point of the interview, the lifetime risk of MDD must be even higher than what has been reported.

What is to be made of these alarmingly high prevalence rates? On the one hand, it is possible that MDD is an even greater public health concern than is generally appreciated, as the prospectively assessed lifetime prevalence of MDD is 2–3 times greater than the

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retrospectively assessed prevalence (Moffitt *et al.* 2010). If MDD such a deleterious condition, however, it is somewhat puzzling that most individuals fail to report depressive episodes. This difference between retrospective and prospective assessments is not present in inquiries of physical health disorders such as diabetes, hypertension or arthritis (Takayanagi *et al.* 2014*b*). Demographic features like old age have been associated to failure to recall MDD status (Takayanagi *et al.* 2014*b*). However, depressive episodes have been described as 'scarring', with the potential to change the individual's personality. Thus it seems unlikely that a poor memory accounts for why most individuals fail to recall meeting MDD criteria.

A possible account for the discrepancy between prospectively-assessed and retrospectively assessed lifetime prevalence rates is that many individuals experience depression as one of many 'homeostatic responses to internal or external stimuli that do not represent true psychopathologic disorders' (Regier *et al.* 1998, p. 114), and as such do not report them as part of their psychiatric history. Lending support to this hypothesis, individuals often fail to report depressive symptoms that they perceive as associated to stress or medical conditions (Eaton *et al.* 2000). The idea that the diagnosis of MDD conflates individuals who are very ill with those who might be experiencing normal, and perhaps even adaptive responses, has been raised as a major concern (Horwitz & Wakefield, 2007; Parker, 2007*a*; Shorter, 2013). A common retort to these arguments is that whereas MDD might seem episodic, common, adaptive and overrecognised, it is in fact chronic, recurrent, maladaptive and underrecognised (Hickie, 2007). The existing data, however, support both views.

Duration and recurrence

According to the DSM 5, one of the features of MDD that makes it pathological and distinct from normal states of negative affect is its prolonged duration (American Psychiatric Association, 2013). Perhaps as a corollary, depressive episodes are believed to be long-lasting. For example, Joiner (2000) cites Shapiro & Keller (1981) in reporting that the median duration of major depressive episodes (MDEs) is 8 months. It is also widely believed that MDD is highly recurrent such that individuals who recover from an episode are still considered to be at a very high risk for future episodes. For example, in a paper preceded by the quote '[s]ingle episodes are extremely rare if the period of observation is significantly extended', Mueller *et al.* (1999) reported that 85% of individuals in a sample who recovered from an index episode had experienced

a recurrence by the end of a 15-year follow-up. Both of these estimates come from analyses of the NIMH Collaborative Study of the Psychobiology of Depression and are widely cited because studies with such long follow-ups are few and far between. Taken together, these estimates suggest that MDD can be a disorder of a prolonged and highly recurring course.

However, as has been noted by Eaton *et al.* (1997, 2008), estimates of the chronicity and recurrence of MDD that come from clinical samples do not generalise to most patients who meet MDD criteria. Data from studies in naturalistic European and North American samples suggest that about half of individuals recover from a MDE within a period of 3 months and most (about 75%) experience recovery in a 3–6-month period (Eaton *et al.* 1997, 2008; Spijker *et al.* 2002). Thus, long-lasting depressive episodes appear to be quite rare (see also Patten *et al.* 2010). Although recurrence rates from long-term follow-ups of population-based studies are lacking, the few studies there are suggest that single-episode MDD is more common than recurrent MDD. In one of the longest follow-up studies to date, Eaton *et al.* (2008) reported that, in a 23-year period, about 35% of individuals experienced recurring depression and 15% experienced an unremitting course. Thus, half of the individuals recovered from their episode within 3–6 months and did not go on to have another episode. Similar findings were produced by a 30–39-year follow-up of a European cohort (Mattisson *et al.* 2007), suggesting that significantly extending the observation does not lead to substantially higher rates of recurrence (see also Steinert *et al.* 2014).

Placebo responses

Another piece of data that bolsters the claim that the diagnosis of MDD can apply to individuals with a wide range of clinical profiles is the diversity and multiplicity of treatments available for depression. On the one hand, there are treatments for intractable cases which include electroconvulsive therapy and transcranial magnetic stimulation. These treatments share the features of acting directly on the brain and requiring extensive medical intervention. At the other extreme there are efficacious treatments for MDD, which are not very intensive. These include unguided self-help (Cuijpers *et al.* 2010) and physical exercise (Babyak *et al.* 2000).

The most widely recommended and researched treatments for MDD, however, are antidepressants and psychotherapy. Reviews of the literature suggest that about 40–60% of individuals respond to antidepressants or psychotherapy (Walsh *et al.* 2002; Cuijpers *et al.* 2014). This leaves a sizeable proportion of patients who are

treatment non-responders. However, it is also note-worthy that around one-third of the patients who are randomised to placebo controls experience clinically significant improvement (Walsh *et al.* 2002; Cuijpers *et al.* 2014). Meta-analytic reviews and aggregation of data from multiple studies suggest that antidepressants are only superior to placebos for individuals with very severe forms of depression (Khan *et al.* 2002; Kirsch *et al.* 2008; Fournier *et al.* 2010; Barbui *et al.* 2011) and analogous findings have emerged in regards to the efficacy of psychotherapy (Driessen *et al.* 2010). Taken together, these findings suggest that the active treatments for depression are only superior to presumably inert placebos and control conditions for the minority of individuals who have severe or very severe MDD. Caution must be taken when considering severity in relation to treatment response, given that other variables such as chronicity and recurrence also predict treatment response (Hollon *et al.* 2014). However, there is evidence that a high placebo response rate in depression trials is present even in patients with more complex clinical pictures (Brunoni *et al.* 2009). Moreover, the placebo response seems to be increasing over time (Walsh *et al.* 2002), a finding that has been replicated and seems accounted for, statistically, by an increase in the heterogeneity of patient samples (Rief *et al.* 2009). It is not difficult to piece together the increase in placebo response with the arguments about the MDD criteria becoming overly inclusive.

Although the placebo response in MDD has often been attributed to non-specific relief that is not thought to endure, most patients who respond to placebos actually stay well (Khan *et al.* 2008). Additionally, studies on the long-term course of untreated depression suggest that the outcomes of individuals who do not receive treatment for depression are comparable with the long-term outcomes of individuals who are treated with antidepressants (Hughes & Cohen, 2009), again a somewhat puzzling findings if we assume most cases of MDD to be either severe, chronic, recurrent or treatment-resistant.

Patients in clinical trials are (self-)selected on the basis on severity and perceived need for treatment. That even these patients experience a substantial placebo response is consistent with the view that some individuals who meet MDD criteria may better be understood as experiencing normal reactions to life stressors that are self-ameliorating.

Diagnosing and treating depression

Depression is very clearly a significant public health concern. The amount of money that is spent on, as well as is lost to, symptoms of depression clearly

attests to this. Highly chronic, frequently recurrent and treatment-resistant depressions are all real phenomena. However, the extremely high prevalence rates that have been reported in prospective studies 'strain credulity' and 'undermine the [diagnostic] model's credibility' (Parker, 2008, p. 842). The evidence reviewed suggests that 35–50% of people will meet the criteria for MDD at some point in a 20–30-year period (Wilhelm *et al.* 2006; Moffitt *et al.* 2010; Rohde *et al.* 2013; Angst *et al.* 2015). It would not be unreasonable to conclude from these data that if a population of individuals were followed indefinitely and assessed more frequently, most would meet criteria for MDD at some point in their life. Most of these episodes would be brief (Eaton *et al.* 1997, 2008; Spijker *et al.* 2002; Patten *et al.* 2010) and many individuals would not experience another episode (Eaton *et al.* 1997, 2008; Mattisson *et al.* 2007; Steinert *et al.* 2014). Most would not seek treatment, which is just as well because many would probably not receive treatment it even if they did seek it. Of those who did seek treatment and were able to obtain it, a sizeable amount would have experienced about the same clinically significant and long-lasting improvement from a sugar pill. This state of affairs is almost impossible to reconcile with a somewhat alarmist view that MDD is best, and perhaps only, understood as being underdiagnosed or underdetected.

Although it may not be appropriate to say that depression is underdiagnosed, it is also not appropriate to simply say that MDD is overdiagnosed. A Goldilocks retort that depression is appropriately diagnosed is obviously not a fair characterisation either. Instead, it seems to be the case that depression is both over- and underdiagnosed. For example, Mitchell *et al.* (2009) reviewed 41 studies on the detection of depression in primary care and found that general practitioners (GPs) only correctly diagnosed depression in about half of patients who met the criteria. They failed to identify depression mostly in patients who had milder symptoms. However, these authors also found that the most common mistake GPs made was diagnosing depression in patients who did not meet the criteria. Thus, at least in primary care, it appears that depression is both over- and underrecognised. These findings should not be dismissed under the assumption that different findings would be obtained in more specialised settings. The diagnostic practices in primary care are very telling of the state of outpatient depression treatment because most treatment for MDD, namely prescription of antidepressants, occurs in the context of primary care (Wun *et al.* 2011).

In the USA, there are clear data evidencing that patients are increasingly being prescribed

antidepressants without receiving a diagnosis of MDD from their physicians, a practice that is more common among GPs than psychiatrist (Mojtabai & Olfson, 2010). It is not just that patients meet MDD criteria but are not diagnosed as such by their GPs. Rather they do not and have never met MDD criteria. For example, Mojtabai & Olfson (2008) reported that, in the USA, only 43% of those currently treated with antidepressants by a GP met the 12-month criteria for a mood or anxiety disorder. In one nationally representative sample, one out of four individuals currently on an antidepressant had never even met the retrospectively assessed criteria for a mood or anxiety disorder at any point in their life (Pagura *et al.* 2011). In a study that used prospective assessments, about 70% of individuals who took antidepressants never met criteria for MDD and around 40% never met criteria for any of the so-called 'common' mood or anxiety disorders assessed (Takayanagi *et al.* 2014*a*). Antidepressants are prescribed in the absence of psychiatric diagnoses for patients who present with subthreshold symptoms as well as those with generalised psychosocial issues or non-specific somatic complaints (Salmon *et al.* 2006; Pagura *et al.* 2011). Discussing these studies, Pagura *et al.* (2011) concluded that 'antidepressant use is becoming concentrated among people with less severe and poorly defined mental health conditions' (p. 1441).

Future recommendations

Attention has been called to the fact that most research on depression has focused on its chronic and recurrent forms (Monroe & Harkness, 2011, 2012). A focus on chronic and recurrent depressions has led to an inability to identify what it is exactly that keeps cases from having a more benign course. In addition to research focusing on less chronic and recurrent depressions, more research is needed to understand milder cases, as well at those that seem to be placebo-responsive.

Depression is heterogeneous both in its symptomatic presentation and its prognosis. It is unsurprising then that whereas some prominent commentators have referred to it as the 'common cold of psychopathology' (Seligman, 1975, p. 75), others have emphasised its 'severe, relapsing, and chronic' nature (Judd *et al.* 2000, p. 1501). Although the current diagnostic criteria for MDD have been extensively criticised, discontent appears to be at an all-time high (Greenberg, 2013; Frances, 2014). In this context, in the USA, the National Institute of Mental Health has called for a new empirically derived and biologically based classification system informed by their Research Domain Criteria. Their priorities include a characterisation of the neural bases of depression and the identification of vulnerability genes. Identifying vulnerability genes is an important task. However, given the heterogeneity of depressive presentations, knowing that someone is at risk for MDD can be of limited value, especially if around half of the population is at risk. What are needed are attempts to predict more clinically relevant variables such as severity, chronicity, recurrence and treatment response. Indeed, limited evidence suggests that whereas the overall heritability of MDD is relatively modest, its more severe and recurrent forms are more highly heritable (Lyons *et al.* 1998; Sullivan *et al.* 2000).

A characterisation of neural functioning in patients with depression is also likely to be a major contribution to our understanding of mood pathology. However, the pattern of neural activation seen in MDD patients often overlaps with the neural patterns that healthy controls exhibit after sad mood inductions (Andrews & Thomson, 2009). Thus, the more informative characterisations of depression are likely to be those that differentiate patients who are depressed from those who are experiencing transient states of sadness. Along these lines, Wakefield *et al.* have brought attention to the need to focus on symptoms of depression that are not mere indicators of distress but are instead pathosuggestive (e.g., Wakefield *et al.* 2007; Wakefield & Schmitz, 2013; Wakefield & Schmitz, 2014). A prolonged duration, thoughts of worthlessness, psychomotor retardation and psychoticism have emerged as useful variables in this regard. Parker (2007*b*) has proposed a model of depression where psychomotor disturbances and psychoticism play a key role as variables that distinguish pathological affective states from more generalised distress. Malhi *et al.* (2005) suggest a tiered model of depression as involving an additive dysfunction of monoamines, starting with serotonergic disturbances for more generalised states of negative affect and including noradrenergic and dopaminergic disturbances for psychomotor retardation and psychoticism, respectively. Examinations of these and other theories of specific pathologies are likely to be more effective than general contrasts between healthy individuals and those who meet criteria for MDD.

Depression can be conceptualised as involving the hyperactivation of negative emotional systems, especially those involved in reactions to losses, and diminished activation of positive emotional systems, especially those involved in reward processing. However, the determination of whether an emotional reaction is excessively or deficient relies on a consideration of the context in which it occurs (Horwitz & Wakefield, 2007). Emerging research suggests that, like the symptoms of depression, the context in which depressive symptoms occur can also be reliably evaluated (Parker *et al.* 2012). Prospective studies exploring the association between the context,

prognosis and pathophysiology of depressive states are needed. Even if these studies cannot provide conclusive evidence regarding the demarcation between pathological states of depression and adaptive states of sadness, they can shed light on the heterogeneity of depressive presentations.

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