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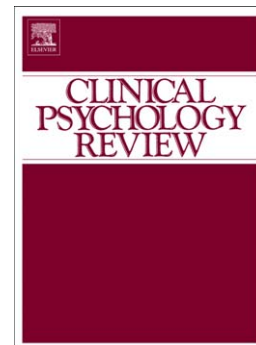
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Prevalence and Clinical Course of Depression: A Review

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Abstract

Depression is one of the leading causes of disease worldwide. Historically conceived as either a disease of the mind or of the brain, treatment options followed this etiology. Current diagnostic assessment of depression is based on descriptions of symptoms, their presence and magnitude over time. Epidemiological studies demonstrate that depressive disorders are highly prevalent: displaying high rates of lifetime incidence, early age onset, high chronicity, and role impairment. These studies have deepened our understanding of the course of depression; remission, recovery, relapse and recurrence. An illustration of recovery rates has begun to demonstrate the complexity of the nature and course of depression. The majority recover; however, recovery may not be permanent and future episodes carry the threat of chronicity. A key variable influencing rates of recovery, relapse, and recurrence is the presence of medical or psychiatric comorbid illnesses. The review considers the literature on Major Depression beginning with a brief historical overview, its classification, and a synthesis of the current knowledge regarding prevalence and course.

Keywords: Depression, Epidemiology, Remission, Relapse, Recurrence

Prevalence and Clinical Course of Depression: A Review

Depression is one of the most commonly diagnosed mental disorders among adults. Our understanding of the course and nature of depression has changed significantly in the last twenty years. From being seen as an acute and self-limiting illness, to a growing clarity that for many depression is now considered a chronic, lifelong illness. Prevalence of depression is of concern, as the cost that depression exacts is considerable. It is not only economically detrimental, but also engenders significant personal and interpersonal suffering alongside its societal impact (Johnson, Weissman, & Klerman, 1992). This review considers the literature on Major Depression beginning with a brief historical overview, its classification, and a synthesis of the current knowledge regarding prevalence and course.

Historical Development

Historically, mood disorders have been conceived as either “organic” or “reactive,” as found in the Diagnostic and Statistical Manual of Mental Disorders-First Edition (DSM-I) (American Psychiatric Association [APA], 1952). The second edition of the manual (DSM-II) (American Psychiatric Association [APA], 1968) continues this basic distinction using the terms “psychotic” and “neurotic.” Mood disorders were understood as either a disease of the brain and organic, or neurotic and therefore a disease of the mind (Boland & Keller, 2002). Disorders of a neurotic or reactive variety could be cured once the cause was removed. Those of a psychotic or organic nature were viewed as having a less favourable outcome. Considered chronic, their fate was institutionalisation combined with somatic treatment. The prevailing understanding left no room outside of the categories curable or chronic.

The Diagnostic and Statistical Manual of Mental Disorders-Third Edition (DSM-III) (American Psychiatric Association [APA], 1980) favoured a descriptive

approach, whereby individuals were diagnosed with a mood disorder based on whether or not they met clear diagnostic criteria, which was based on a constellation of symptoms and specific duration. The goal of treatment was symptom reduction or extinction if possible. However, treatment outcomes including continued relapse and recurrence posed challenges to developing adequate treatments. It became clear that the effectiveness of interventions was reduced without the context of natural course informing them. From the 1980's onwards, long-term studies on the course of depression and outcomes in patients began to be reported (Angst, 1986).

Classification

The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV-TR) (American Psychiatric Association [APA], 2000) describes a Major Depressive Disorder (MDD) diagnosis based on the presence of a specified number of symptoms with a precise duration. Primarily symptoms of either depressed mood or loss of interest or pleasure are present. Additionally the criteria of at least five items from the DSM-IV-TR (APA, 2000) list need to be present for a duration of two weeks and as such, represents a change from previous functioning. It includes depressive mood and loss of interest in most activities, appetite and sleep disturbance, feelings of worthlessness and guilt, suicidal thoughts and ideation.

The DSM-IV-TR (APA, 2000) describes Dysthymic Disorder as chronic and symptoms should not be as severe as that for MDD, but present for at least two years. It includes symptoms of depressed mood for most of the day, and at least two of the following: poor appetite, insomnia, low energy, poor self-esteem, lack of concentration and feelings of hopelessness. If an individual is symptom-free for two months or more, then it is not diagnosable. Double depression is dysthymia with MDD.

The DSM-5 will be published in 2013 and like the DSM-IV-TR (APA, 2000) it continues the diagnostic distinctions of MDD and dysthymic disorder. However, the latter is renamed as Chronic Depressive Disorder (CDD). For DSM-5 the criteria for diagnosis of these disorders remains the same as DSM-IV-TR (APA, 2000). The DSM-5 proposes additional diagnostic categories such as mixed Anxiety/Depression and also integrates childhood and adolescent psychiatric disorders into relevant chapters (see, <http://www.dsm5.org>).

The World Health Organisations` (WHO) International Classification for Diseases and Related Disorders (ICD-10) describes the criteria for a depressive episode, where at least four items, such as loss of interest in activities, lack of emotional reactions, sleep disturbance, loss of appetite, motor retardation, weight loss, loss of libido, and decreased energy are present for a duration of two weeks (World Health Organization [WHO], 1993). Dysthymia is described as “a period of at least two years of constant and constantly recurring depressed mood” (WHO, 1993, p.104). Symptoms are not as severe or persistent as recurrent depression, but intervening periods of normal mood rarely last for longer than a few weeks. At least three symptom items from the list above are present during these periods, including items such as, often in tears, difficulty concentrating, loss of confidence and feelings of inadequacy and hopelessness, inability to cope, and despair about the future.

The difference that exists between the two classification systems described is associated with the lower threshold of symptom requirements for ICD-10 (WHO, 1993) compared to DSM-IV-TR (APA, 2000). However, high concordance has been demonstrated between both classifications systems for depressive episode and dysthymia (Andrews, Slade, & Peters, 1999). The definitions could be made identical

as the differences do not produce significant numbers of discrepant diagnoses (Andrews et al., 1999).

Epidemiology of Depression

Several major epidemiological studies have been carried out to determine the prevalence of depressive disorder in the general population. Two such large scale surveys from the U.S. are the Baltimore Epidemiologic Catchment Area Survey (ECA) (Eaton et al., 1989) and the National Comorbidity Survey (NCS), initially conducted in 1991 and replicated in 2001 (Kessler et al., 2003; Kessler et al., 1994). Using the Diagnostic Interview Schedule (DIS) (Robins, Helzer, Croughan, & Ratcliff, 1981) based on the DSM-III (APA, 1980), the ECA surveyed 18,571 households and 2,290 institutional residents aged eighteen years and older. In general terms the data from this survey reveals that in any 6-month period, 19.5% of the adult U.S. population, or 1 in every 5 persons eighteen years and above, suffers with a diagnosable mental health disorder (Bourdon, Rae, Locke, Narrow, & Regier, 1992). In detail, the ECA survey reports 1-month (5.2%), 6-month (5.8%), 12-month (6.3%), and lifetime prevalence (8.3%) of depressive disorder in the population (Bourdon et al., 1992).

The National Comorbidity Survey (NCS) epidemiologic investigation was designed to study prevalence of Diagnostic and Statistical Manual of Mental Disorders-Third Edition Revised (DSM-III-R) (American Psychiatric Association [APA], 1987) disorders and associated use of health and mental health services. The survey administered the WHO Composite International Diagnostic Interview (CIDI) (Robins et al., 1988) to a sample of over 8,000 respondents. The NCS report a 12-month prevalence of 8.6% and a lifetime prevalence of 14.9% of depressive disorder in the population (Kessler et al., 1994). Like the earlier ECA study they also report on the early age onset of depression. These figures are higher than those reported by the earlier

ECA survey. However, the NCS did lower the age range to fifteen as opposed to eighteen years and given that they noted the early age onset, perhaps the extension allowed for this to be recorded with more accuracy. The high prevalence estimates found in both the ECA and NCS surveys was a cause of concern. At the time the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)(American Psychiatric Association [APA], 1994) was being prepared that would emphasise the importance of considering the clinical significance of symptoms within diagnostic criteria for depressive disorder.

Based on the publication of the DSM-IV (APA, 1994), a new National Comorbidity Survey-Replication (NCS-R) was administered, using the CIDI (Robins et al., 1988). The prevalence reported for depressive disorder in the population was 16.2% for lifetime and 6.6% for 12-month prevalence (Kessler et al., 2003). The rate for 12-month prevalence is slightly higher than the rate reported in the earlier ECA survey (6.3%), but lower than the rate reported in the first NCS survey (8.6%). The reported rate for lifetime prevalence is higher than that reported in the earlier NCS (14.9%) and also the ECA surveys (8.3%). A plausible explanation might be that the increasing prevalence reflects a finding first noted in the 1980's related to the increased incidence of depression among younger age cohorts (Burke, Burke, Rae, & Regier, 1991). Other plausible explanations are an increased willingness to report and a general increase in accurate reporting, aided by methodological advances in data collection instruments and interview schedules developed in stem-branch format. Stem-branch format allows a question to be asked and then follow-up questions to support and add detail to the initial answer given (Kessler, Wittchen, Abelson, & Zhao, 2000).

The structured interview instruments used in the different studies were based on different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM)

(APA, 1980, 1987, 1994) and it is the case that the clinical significance of symptoms have become more refined over time. Additionally, developments in methodology such as stem-branch format, aided the accurate diagnosis of symptoms. Consequently the structured interview instruments have become more refined and robust over time. Still, the sensitivity and specificity of the instruments used in the ECA and NCS epidemiological reports have been criticised for potentially overinflating the prevalence of depression (Narrow, Rae, Robins, & Regier, 2002). The reported prevalence rates of between 6%-9% for MDD and for dysthymic disorder between 3%-6% were revised and values for clinical significance returned figures of between 4.6%-5.4% for MDD and 1.7%-1.8% for dysthymic disorder (Narrow et al., 2002).

A point of interest and concern is the location of the onset of depression as a feature of younger age groups, combined with the likelihood of recurrence throughout adulthood (Gotlib & Hammen, 2002). Based on results from these epidemiologic studies (Kessler et al., 2003; Kessler et al., 1994; Regier, Boyd, Burke, & Rae, 1988) of the U.S. population it is clear is that depression is frequent in the general population. What is also clear is that depression ranks higher among the leading causes of disease burden for women than for men (Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). Prevalence rates and gender differences are relatively constant across the adult lifespan and given the earlier age onset suggests that lifetime prevalence will be higher in the future for younger cohorts (Craighead, Sheets, Brosse, & Ilardi, 2007).

Outside of the U.S., the World Health Organisation (WHO) has demonstrated that depressive disorders are one of the leading causes of disease worldwide. The reported prevalence throughout the world of depressive episodes is 16 per 100,000 per year for males and 25 per 100,000 per year for females (Üstün et al., 2004). Their results show depression as the fourth leading cause of disease burden in the world

accounting for 4.4% of total disability adjusted life years (DALY) (Üstün et al., 2004). DALY is a construct employed to quantify objectively the disease burden (Murray, 1996).

The WHO highlight the occurrence of depression in younger age groups (20-25 years). Based on data from the NCS-R, half of all lifetime cases of mood disorders start at 14 years and three-fourths by 24 years (Kessler et al., 2005). One review of the literature posits the peak years for onset to be between 15-29 years of age (Craighead et al., 2007). Epidemiological surveys have highlighted the shift for early age onset combined with increased prevalence in younger age periods. Analysis of the data from the ECA demonstrates a gradual shift to increased rates for major depression between the ages of 15 and 19 years (Burke et al., 1991).

Zisook et al. (2007) report that earlier age onset of major depression effects the course and is associated with greater illness burden across a wide range of indicators compared to those with later ages at onset. These indicators include: never being married, social and occupational impairment, poorer quality of life, greater comorbidity both medical and psychiatric, a more negative outlook, a greater number of depressive episodes alongside increased symptom severity, and increased suicidal ideation and attempted suicide (Zisook et al., 2007). Consequently depression is a major health problem for which it is important to develop treatments and the occurrence in younger age groups highlights the need for early intervention.

The WHO report that in Europe, the prevalence of depressive episodes for males is 16 per 100,000 per year and for females is 27 per 100,000 per year. This data includes information collected from fourteen European countries (Üstün et al., 2004). A recent report estimates that depression accounts for 6% of DALY (Sobocki, Jönsson, Angst, & Rehnberg, 2006). A cross-sectional community study by the European Outcome of

Depression International Network (ODIN) (Ayuso-Mateos et al., 2001) included urban and rural areas within Ireland, Spain, the U.K., Norway, and Finland. Using a stratified design where first the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was employed and thereafter the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization, 1994), the survey reports a 12-month prevalence of depressive disorders of 8.56%. Similar to the WHO survey, depressive disorder was defined in two ways based on both the ICD-10 (WHO, 1993) and the DSM-IV (APA, 1994). The global sample comprising the five countries returns a weighted mean 12-month prevalence of 6.6% (CI: 5.4-8.4) for depressive episode as assessed by the ICD-10 (WHO, 1993), and as assessed by the DSM-IV (APA, 1994) a weighted mean 12-month prevalence of 6.7% (CI: 5.4-8.2). Given the concordance between these classification systems (Andrews et al., 1999) it is not surprising that they return similar percentages.

In the ODIN study the 12-month prevalence rate of 8.56% is exactly the same as the 12-month reported prevalence in the initial NCS study (8.6%), but higher than what is reported in the 12-month prevalence NCS-R survey (6.3%). The survey confirms the prevalence of greater burden of depression in women (10.05%) than men (6.61%) (Bebbington et al., 1998) and demonstrates that depressive disorders are highly prevalent among adults in Europe.

Another European study (Copeland et al., 2004) reports on prevalence of depression in subjects aged 65 and older. This survey complements the earlier ODIN survey whose age range included 18-64 years. The 12-month prevalence reported across the European centres was 12.3%. The survey further supports the gender divide literature, giving overall prevalence of depression of 14.1% for women and 8.6% for men (Bebbington et al., 1998; Ohayon, Priest, Guilleminault, & Caulet, 1999).

Epidemiological studies highlight magnitude of the problem and also uncover the extent of co-morbidity. The U.S. epidemiological studies (ECA and NCS) found that up to 75% of cases display at least one of the other DSM (APA, 1980, 1987, 1994) classified disorders (Kessler et al., 1994; Robins & Regier, 1991). Patients with a diagnosis of major depression and a coexisting DSM (APA, 1980, 1987, 1994) classified disorder, report significantly poorer psychosocial functioning and poorer recovery rates over 12-months compared with patients who have a single diagnosis of depression (Keitner, Ryan, Miller, Kohn, & Epstein, 1991).

The strongest comorbidity is with the anxiety disorders of one form or other. Comorbid anxiety disorders are present in 50% of subjects with major depression (Fava, 1997). A similar level of comorbid anxiety with major depression is also found in nonclinical samples (Wittchen & Jacobi, 2005). Comorbidity is associated with greater severity of depressive symptoms, and lower treatment response rates (Young, Mufson, & Davies, 2006), alongside greater social and occupational impairment (Anseau et al., 2008). The association with depression is particularly strong for post-traumatic stress disorder, generalized anxiety disorder, obsessive-compulsive disorder, and social phobia (Brown, Campbell, Lehman, Grisham, & Mancill, 2001). The Zurich study notes higher prevalence of depression and panic disorder reporting that 12% of their sample displayed comorbidity (Volirath & Angst, 1989). Comorbidity has been established with other forms of depression such as major depression combined with dysthymia referred to as 'double depression' (Keller, Lavori, Lewis, & Klerman, 1983; Keller & Shapiro, 1983), personality disorders (Reich & Green, 1991) and substance abuse (Mueller et al., 1994). Comorbidity has also been established between depression and physical conditions such as cardiovascular disorders, respiratory syndromes, diabetes,

HIV, irritable bowel syndrome, and stroke (Angst, Gamma, Rossler, Ajdacic, & Klien, 2009; Rosenthal, 2003; Wells et al., 1989).

Many of the large epidemiologic surveys report on duration of depressive episodes. Understanding duration can help in understanding the very nature of depression and consequently inform the development of effective treatment strategies. The first Worldwide survey of the Global Burden of Diseases (GBD) estimated average episode duration to be 6 months (Murray & Lopez, 1996). This estimate compares favorably to the overall mean reported by the ECA study of 6.5 months and also the NCS-R survey reporting an overall mean of 5.5 months duration. A 12-year follow-up of the ECA survey reports a mean duration of 6.75 months, irrespective of gender (Eaton et al., 1997). The most recent report of the ECA 23-year follow-up states a median episode length of 3 months (Eaton et al., 2008). A three month median is reported by the NEMESIS survey, which also reports a mean time to recovery of 8.4 months (Spijker et al., 2002). As well as a high prevalence in women, duration is often longer for females than for males (Ayuso-Mateos et al., 2001; Bebbington et al., 1998; Üstün et al., 2004).

Differences in reported duration can exist because different definitions of recovery were utilised. Also mean duration reported in clinical population studies is different from that in general population studies. Differences caused by methodological difficulties with some studies also feature, for example, data have been gathered at different times from participants, or data has been gathered from selected populations. Both these can impact on outcome and generally bias the research towards an overrepresentation of chronicity (Spijker et al., 2002). It needs also to be remembered that duration of a depressive episode is influenced by a large host of variables, such as whether someone is living with a partner, the severity of the depressive case and

whether comorbid dysthymia is present (Keller, Shapiro, Lavori, & Wolfe, 1982; Mueller et al., 1996), whether one is unemployed, or for example if a person has experienced a recent bereavement (Ohayon et al., 1999).

The NEMESIS survey also reports that episodes of longer duration were found to exist with comorbid dysthymia and increased severity, whereas episodes that were of shorter duration were characterised as being recurrent (Spijker et al., 2002).

Comorbidity and other confounding variables, such as severity of the episode and number of previous episodes, can have the impact of almost doubling or more the duration of the depressive episode. Whereas if the episode is recurring this trend can be reversed (Spijker et al., 2002). This latter point differs from the clinical population of the National Institute for Mental Health (NIMH) study, where duration of recurrent episodes was similar (Solomon et al., 1997). This may therefore only be a feature of general population surveys (Eaton et al., 1997).

The Cost of Depression

Overall the picture painted is similar across the surveys of prevalence throughout the world. Data clearly identify depression as a major public health problem (Scott & Dickey, 2003). Depression exacts a huge cost on the individual and their personal circumstances. It contributes to enormous loss for society as well.

A recent economic review of the cost of depression reports that the direct cost of depression is accounted for by high healthcare usage, the majority of which is not the result of depression treatment costs, but other healthcare costs (Donohue & Pincus, 2007). The economic burden is further added to by the indirect cost of depression and associated morbidity such as, losses in quality of life, absenteeism and decreased productivity, and functional impairment in many other personal and interpersonal areas of life (Donohue & Pincus, 2007). The indirect cost also accounts for increased

mortality, in particular depression related suicide. Depression significantly increases the risk of other causes of mortality as well (Donohue & Pincus, 2007).

In the U.S. for the year 2000 the economic burden of depression was estimated at \$83.1 billion. Thirty-one percent (31%) related to direct medical costs, 7% related to mortality costs, and 62% to workplace costs (Greenberg et al., 2003). In Europe for the year 2004 the annual cost of depression was estimated at €118 billion. Direct healthcare costs amounted to 36% and indirect costs due to morbidity and mortality amounted to 64% (Sobocki et al., 2006).

The direct costs are substantial and several studies have demonstrated higher healthcare costs with depressed patients than those without depression, and for depressed patients compared to patients with other illnesses (Druss, Rosenheck, & Sledge, 2000; Simon, Ormel, VonKorff, & Barlow, 1995). Comorbidity and treatment-resistant depression further add to the cost burden (Chrisholm et al., 2003; Russell, Hawkins, & Ozminkowski, 2004). The reasons are complex and increased costs may be due to, for example, a tendency to amplify symptoms (Katon & Ciechanowski, 2002). Depression can negatively impact self-care and this may in turn worsen the course of medical conditions and consequently lead to higher healthcare usage and costs (Donohue & Pincus, 2007).

The indirect costs too are substantial, particularly morbid absenteeism and loss of economic productivity, and mortality, chiefly suicide. Consistently, studies have found a relationship between depression and work impairment (Kessler, Greenberg, Mickelson, Meneades, & Wang, 2001; Stewart, Ricci, Chee, Hahn, & Morganstein, 2003). Greenberg et al. (2003) estimated cost of absenteeism and presenteeism (reduced productivity at work) at \$52 million in the year 2000. Of course, such an estimate does not include all productivity costs, such as increased risk of workplace injury, or levels

of productivity among family members of persons with depression (Donohue & Pincus, 2007).

A recent study, where 48% of depressed patients had suicidal ideation and 24% of those had made a suicide attempt, report not receiving or even recognising the need for treatment (Pagura, Fotti, Katz, & Sareen, 2009). Holma et al. (2010) report the incidence of suicide is highest during major depressive episodes. However, previous attempts and poor social support also indicate short-term risk and long-term risk are determined by the length of time spent depressed (Holma et al., 2010). It is often the case that completed suicides and attempted suicides have not received adequate treatment (Suominen, Isometsa, Henriksson, Ostamo, & Lonnqvist, 1998). Lifetime suicide rate for persons with depression has been calculated at 15%, however a recent study based on the U.S. population calculates rates to be 7% for males and 1% for females, a combined risk of 3.4% (Blair-West, Cantor, Mellsop, & Eyeson-Annan, 1999). The cost goes beyond the lifetime loss of productivity, but also the cost to those left behind. Greenberg et al. (2003) estimate of depression related suicide mortality cost for the year 2000 (\$5.4 billion), in today's terms would amount to approximately \$7.05 billion (CoinNews Media Group LLC, 2009).

The brief review of cost, demonstrates that the global cost of depression far outweighs the cost to understanding it accurately and treating successfully those who suffer. However, the promise of treatments reducing the burden of depression is conditional on access to appropriate care and the appropriateness of the care delivered, see reviews: (Donohue & Pincus, 2007; Gilbody, Bower, & Whitty, 2006; Wang, Simon, & Kessler, 2003).

The Course of Depression: Remission, Recovery, Relapse and Recurrence

Early empirical studies investigating the course of depression were hindered by a lack of consensus about key points of change that were being observed in the results. This was resolved and the key change points were named and defined by a task force, see Table I (Frank et al., 1991).

Table I about here

What follows is a discussion of the research reports on the course of depression. Three large scale studies to note are firstly, the National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS) (Katz, Secunda, Hirschfeld, & Koslow, 1979), second, the Zurich Study (Angst, 1986; Angst et al., 1973), and thirdly, the Medical Outcomes Study (MOS) (Wells, Burnam, Rogers, & Hays, 1992). The CDS and the Zurich studies are the only prospective long-term studies of the natural course of depression. Participants in the CDS were recruited from individuals who sought psychiatric treatment. The survey recruited participants from several U.S. university hospitals between 1979 and 1981. Participants were then assessed every 6-months for a period of 5 years, and then further assessed annually for a 15 year period. Between 1959 and 1963 the Zurich Study recruited hospitalised patients with a diagnosis of depression. Participants were treated and followed-up every five years for up to 21 years. The MOS survey examined the course of several diseases in a variety of health care settings. Recruitment took place at three different U.S. cities between February and October 1986. Participants were assessed yearly for a period of 3-years.

Remission and Recovery

Remission is a reduction or end to symptoms for a period of time, but generally conceived as shorter than eight weeks, which is considered the point of recovery. A number of early studies began to question the established wisdom about remission and recovery from depression. One study (Kerr, Roth, Schapira, & Gurney, 1972) that followed-up 126 patients who had been hospitalised for depression, showed 60% recovered or improved, but that 6% remained depressed after four years. The study demonstrated that the majority of patients seem to recover 12-months post treatment, but a significant number can continue to experience partial remission or indeed no reduction in symptoms for a number of years. The study also noted that more men showed better outcomes, as did patients with later onset, shorter duration of illness and less impairment.

Findings from other large scale studies validate the claim that most recover within one year from a depressive episode, but that there is a significant minority that do not achieve remission or recover at an early stage and can progress on a chronic course for some years. For example, 13% of participants in the Zurich Study did not recover from their index episode of major depression (Angst et al., 1973). Similarly, in another study (Rounsaville, Prusoff, & Padian, 1980) of 96 patients who met the diagnostic criteria for major depressive disorder, 14% of subjects did not show remission at the end of an initial 4-month treatment with antidepressants and/or psychotherapy. At 16-month follow-up with 72 patients, 9 (12%) patients were still depressed, and 10 (14%) had relapses and had recovered in that time. Overall 53% of the 72 patients followed-up had recovered sufficiently from impairment.

However, the authors also note that in a retrospective global symptom judgement using a 7-point likert scale evaluating individually the previous 12-months, it became clear that only 22 of the 72 patients were entirely symptom free. Twenty-six

reported being depressed with gradual improvement, 10 described as being mostly well over the 12-months, 5 experienced periodic depressive symptoms, 4 reported an increase in depressive symptoms and 5 assumed chronically depressed. Therefore, despite generally favorable findings in the study, only a minority were entirely symptom free during the 12-month follow-up period (Rounsaville et al., 1980). Further, the study highlights the pervasiveness of residual symptoms, a point of significance regarding course of depression (Judd et al., 2000; Mojtabai, 2001). Notably the study shows men showing more favorable outcomes than females, who demonstrate higher risk for onset, longer duration of episodes and higher risk for recurrence. Traditional wisdom is challenged, as these findings are supportive of longer duration to remission and recovery, varied, incremental, and cyclical paths towards remission and recovery, and also, at times, non-recovery. Further supporting evidence on the course of remission and recovery is provided by the NIMH Collaborative Depression Study (CDS).

The CDS study described earlier reports on recovery rates from a clinical sample over the course of a 15-year follow-up period. Their data show there was no significant difference in the rates of recovery between the primary episode and subsequent, second, third, and fourth, episodes of depression. Reporting that almost 8% of participants did not recover after 5 years. They note that the majority (70%) of participants recovered from their index episode of depression within 1-year (Keller et al., 1982). By 2-years 20% had still not recovered, by 5-years 12% were still depressed (Keller et al., 1992), by 10-years 7% had not experienced remission (Mueller et al., 1996) and by 15-years the percentage of participants not recovered was 6% (Keller & Boland, 1998). Only on the fifth episode was there some notable change in the recovery rate, but not significant. The trajectory towards remission and recovery detailed in the 15-year CDS follow-up survey reaffirms the understanding of course of depression in that the majority of those

who experience a primary episode of depression will recover satisfactorily within 12-months. The rate of recovery is slower for subsequent years, but at the same time recovery continues to occur.

The slower pace is influenced by the length of the episode; the longer the episode the less the likelihood of recovery. Median rate of recovery reported by the CDS for year 1 is 67% and this contrasts greatly the median rate for years thereafter of 9% (Mueller et al., 1996). Apart from those who recover within the year, remission for a percentage of patients is varied and incremental. For instance, Keller et al. (1992) report that by 5-years, 12% of patients were still depressed, but a later follow-up reveals that 38% of those patients had recovered by the next 5-years (Mueller et al., 1996). They conclude that for each episode of depression, about 10% remain ill for about 5-years (Solomon et al., 1997), but that by 10-years the majority will have recovered from their primary episode of depression. Based on their observations for 15-years, the CDS provides probability estimates of rates for recovery to be 67% for year 1, 81% recovery by 2-years, by 5-years 88% recovery and by 10-years 93% (Mueller et al., 1996). Despite lengthy periods of illness, people continue to recover (Mueller et al., 1996) and that the course towards remission and recovery seems to level out at between 5-10 years.

In the CDS study, the sample being reported on are clinical and perhaps therefore biased towards an overrepresentation of chronicity (Boland & Keller, 2002). However, a recent analysis of data provided from the ECA general population survey is supportive of clinical findings and notes that about 50% of first episode participants recover with no future episodes, that about 15% experience an unremitting and chronic course, and that 35% go on to experience recurrent episodes (Eaton et al., 2008). The Sterling County Study (SCS) of a community sample also supports the reported clinical

data on course and chronicity (Murphy, 1990). The results suggest that depressions found in the community are similar in seriousness to clinical samples.

Chronicity also influences time to recovery as shown in the CDS study (Coryell, Endicott, & Keller, 1990). Seventy-five percent of those determined as non-chronic recovered within 1-year, where the same percentage of those determined as chronic took 4-years to achieve recovery (Coryell et al., 1990). The MOS study, described earlier, does not alter the perception being generated by the research in this area. Of those with milder depression, almost 65% recovered within one year as opposed to only 54% recovery within 1-year for the severely depressed (Wells et al., 1992). The data from the MOS again supports the finding that a large percentage of people do not recover within a 1-year period. A percentage of individuals never achieves remission, and of those that do, the possibility of relapse is high. It seems that approximately 50%-70% of individuals will recover from a depressive episode within 1-year, between 14-35% will experience periods of recurring depressive episodes, and 6-15% will experience a chronic course of depression over many years.

For those with double depression the CDS study observed improved rates of recovery compared to those diagnosed with major depression. At 12-month follow-up 88% of patients with double depression had recovered, whereas this fell to 69% for those with major depression (Keller, Lavori, Endicott, Coryell, & Klerman, 1983). However, double depression recovery seemed largely to represent a recovery from major depressive episode to dysthymic disorder and not a complete absence of symptoms. In a study on double depression, in a sample of 101 patients, who met the criteria for major depressive disorder and had an underlying chronic depressive disorder for at least two years, showed that their rates of recovery were greatly different from those with only a single diagnosis (Keller & Shapiro, 1983). The recovery rate is lower

for those with compound depression and significantly they also report poorer functioning (Keitner et al., 1991). When recovery is considered as recovery from acute depression, the recovery rate is 89%, but when considered as recovery from both acute and chronic depression the rate is 31% (Keller & Shapiro, 1983). The symptomatic course for double depression and recurrent depression is seen as chronic and variable over time (Judd et al., 1998).

Relapse

Relapse is an early return of symptoms following what appears at least to have been a positive response to treatment. Relapsed individuals meet the full syndrome criteria and it occurs during a period of remission. One early report on relapse from major depressive disorder (Keller et al., 1982) documents a high rate of relapse (25%) after 12-weeks and notably the majority of those (25%) relapsed after 4-weeks. In the CDS study, 22% of those who achieved full remission from their primary episode of depression had relapsed within the year (Keller, Lavori, Endicott et al., 1983). The Group for Longitudinal Affective Disorders Study in Japan (GLADS) report a similar rate of relapse for a 12-month period of 21%, 30% by two years and 42% by five years (Kanai et al., 2003).

Many factors can contribute to relapse and these include a history of depressive episodes, old age, and a history of psychiatric illness. Risk of relapse increases if there is an underlying presence of chronic depression for at least a two year duration (Keller & Shapiro, 1983). Judd and colleagues (Judd et al., 2000) conclude that residual symptoms are a key indicator of a more severe, relapsing and chronic future course of depression (Judd et al., 2000). Data from the ECA community sample verifies this course towards chronicity (Mojtabai, 2001). The most recent contribution to this debate

comes from the CDS (Solomon et al., 2008) and confirms that assessing psychosocial impairment could identify patients less likely to recover from a depressive episode.

A study by Faravelli and colleagues (Faravelli, Ambonetti, Pallanti, & Pazzagli, 1986) where fifty percent of their participants relapsed within 12-months, shows that for some, remission from MDD is only partial and more apparent than real. It is not accompanied by a return of positive indicators of well-being, subjects can display higher levels of residual symptoms and poorer social functioning. A study by Lin and colleagues (Lin et al., 1998) reports a relapse rate of 37% within 12-months for primary care patients. The study (Lin et al., 1998) supports the contention that a history of depressive episodes and residual or sub-threshold symptom presence seven months after treatment, increases by threefold the risk of relapse.

Recurrence

Studies highlight that for many with depression, recurrence after recovery is the rule (Mueller et al., 1999). Possibility of future episodes of depression is as high as 30%, and this rate seems to increase with subsequent episodes. As early as 1976 Weissman and Kasl (Weissman & Kasl, 1976) report that for the most part, patients were asymptomatic at follow-up, but a substantial number had a return of acute symptoms; 60% sought further treatment during the year. Another study (Rao & Nammalvar, 1977) reports that recurrence occurred in 75% of the 109 cases. They observe that the onset of depression before the age of 40, predisposed one to recurrences and an increased risk of chronicity. The Zurich Study data supports high recurrence rates where they found that 75% of participants had more than a single episode of depression (Angst, 1992).

Empirical data from the CDS supports the claim that rate of recurrence increases with subsequent episodes. The CDS reports an initial recurrence rate of between 25-

40% after 2-years. This however increases dramatically over time, up to 60% recurrence after 5-years, 75% after 10-years and 85% after 15-years (Keller & Boland, 1998). The CDS also point out in their research that recurrence also occurred for 58% of subjects who had recovered and remained well for 5-years (Mueller et al., 1999). Characteristics that increased the likelihood of recurrence include, being female (43%), never having married (55%), a history of prior depressive episodes (11%), and longer duration of prior episodes (18%). However, none of these characteristics was determining of the 58% who were recovered and well for 5-years before recurrence (Mueller et al., 1999). It seems that few demographic or clinical factors can be identified with reasonable certainty to predict an individual's likelihood for recurrence. Especially those who have recovered from an index episode and remained well for some time.

At the same time, recurrence after recovery from depression is not always inevitable (Mueller et al., 1999). In their 15-year prospective follow-up, Muller and colleagues, observe that some people do not develop another episode (Mueller et al., 1999). The recurrence trajectory and associated rates over time are alarming and in contrast to rates of recovery which seem to level off after between 5-10 years. The CDS analysis of 481 recurrences in a sample of 318 subjects followed-up for a period of between 5 and 10 years, demonstrate that the median time to recurrence for the first episode was 150-weeks, for the second recurrence 83-weeks, the third was 77 weeks, fourth 68-weeks and the fifth 57-weeks (Solomon et al., 2000). On average, the CDS study reports that individuals who recovered from their index episode of depression suffered two recurrences in the 10-year follow-up period (Solomon et al., 2000). Consistent with the data regarding relapse, if individuals have experienced several previous episodes of depression, their time to recurrence seems to shorten.

A key factor in the rate and timing of recurrence, is the quality of recovery. Individuals in the CDS study who fully recovered, that is, were asymptomatic at follow-up, had much lower rates (66%) of recurrence than did those with some symptoms (87%) at follow-up (Mueller et al., 1999). Other studies support this finding and report that residual symptoms at time of recovery predicted earlier recurrence; the probability of staying well without symptoms is less than 50% for two years or more after recovery (Kanai et al., 2003). The risk of recurrence increases by 16% with each successive recurrence, but consequently decreases with the extension of recovery duration (Solomon et al., 2000). Like relapse of symptoms, recurrence can be influenced by some key risk factors, such as the individuals and their family's history of depressive episodes and their duration, any co-morbidity (for example dysthymia), more vulnerability at older age, and those with poor response to treatment and relapse prevention interventions (Boland & Keller, 2002).

Conclusion

The growing prevalence of depression worldwide is of concern, especially given the associated economic, societal, personal, and interpersonal costs. The global cost of depression far outweighs the cost to understanding it accurately and treating successfully those who suffer. Because depression displays high rates of lifetime prevalence, early age of onset, high chronicity, and role impairment, the WHO has ranked depression as the single most burdensome disease in the world in terms of years lived with disability (Murray & Lopez, 1996). Our understanding of depression has evolved in the last number of decades. The research on prevalence and course demonstrates the complexity of this disorder. Generally it seems that the majority of individuals who experience depression will recover within 1-year. However, a portion may not experience recovery, and show no signs of remission even after 5-years or

more. Lastly, recovery is not permanent and future episodes of depression carry the continued threat of chronicity for the individual (Boland & Keller, 2002). Predictors of relapse and recurrence are largely similar; they highlight the vulnerabilities that can increase risk, such as a history of depressive episodes, residual symptoms and the quality of remission and recovery achieved, among others. They are influential in increasing the potential for relapse during a period of remission and also a recurrence during a period of recovery. A further key variable influencing rates of remission, recovery, relapse, and recurrence is the presence of comorbid illnesses, whether medical or psychiatric. Research from several studies support the claim that the deleterious effects of comorbidity are significant.

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Table I Key change points in depression and their definitions

Key Terms	Definition
Episode	Defined as having a certain number of symptoms for a certain period of time, fully symptomatic. (e.g DSM-IV criteria, see classification)
Remission	Partial remission where the individual is no longer fully symptomatic, but displays more than minimal symptoms. Full remission, is a brief period (2-8 weeks), where the individual is asymptomatic, no more than minimal symptoms
Response	A partial or full remission due to a treatment intervention
Recovery	Defined as a full remission, symptom free for a certain length of time (>8weeks). It designates a recovery from an episode
Relapse	An early return of symptoms following a positive response, meeting full syndrome criteria that occurs during the period of remission
Recurrence	Refers to a new episode, which can only occur during a recovery

Highlights

Epidemiological studies demonstrate that depressive disorders are highly prevalent

Recovery rates have begun to demonstrate the complexity of the nature and course of depression

Relapse and recurrence are key in understanding depression, as they carry the threat of chronicity

A key variable influencing recovery is the presence of comorbid illnesses, medical or psychiatric

The global cost of depression far outweighs the cost to treating successfully those who suffer