Comorbidity

Symptoms, Conditions,
Behavior and Treatments

Edited by
Rhonda Brown
Einar Thorsteinsson

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Preface

Collectively, as co-authors, we have extensive clinical and research experience related to the various clinical disorders, symptoms, behaviour and biology covered in the book. Furthermore, as research collaborators, we can provide a unique perspective on the likely evolution and nature of disease comorbidity, which integrates biological, medical and psychological perspectives. The book was written with an academic audience in mind, although other interested individuals may appreciate the exploration of possible mechanisms underpinning disease comorbidity. To be clear, this is *not* a self-help book that reflects upon the way in which people should live a better life or which reflects upon the way that we as individuals live our own lives.

The stimulus for the book was research conducted by Laird Birmingham, Rhonda Brown and others, related to low body temperature and infection in anorexia nervosa patients, which later gave rise to discussions around the possible role played by body temperature in mediating some of the adverse health outcomes related to overweight/ obesity. However, more broadly, the co-authors have worked collectively, in several different research groups, to answer the following questions related to disease comorbidity: What is causing the comorbidity

between different medical and psychological conditions? What role (if any) is played by the shared (or overlapping) medical and psychological symptoms? Or is a common factor more likely to cause the co-occurrences? Finally, why is a similar profile of risk factors detected for a range of different but frequently comorbid illnesses and conditions?

As argued in this book, there is a crucial need to more fully integrate a broader range of comorbid illnesses and conditions, and their often overlapping risk factors, into the same disease models; to arrive at a more complex real-world understanding of comorbid illness causation. If such a clinical model could be developed, it might be used to test complex hypotheses related to the evolution and nature of disease comorbidity as well as evaluate potential new therapies.

Finally, as co-authors, we wish to thank the various researchers and clinicians we have worked with over many years, who each have contributed to the evolution of the thoughts that are collectively advanced in this book.

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Notes on Contributors

C. Laird Birmingham, M.D. is a Specialist in Internal Medicine, Epidemiologist and Biostatistician and a Professor of Psychiatry at the University of British Columbia, where he was previously Professor of Medicine. He was Leader of the BC Eating Disorders Epidemiology Project in the Centre for Health Evaluation and Outcome Sciences until 2008 and then Medical Director of the Woodstone Residential Treatment Centre for Eating Disorders until December 2013. He is a Member of the Brain Research Centre at UBC and Senior Associate Clinician Scientist at the Children and Family Research Institute. He has more than 40 years of experience in eating disorder research and treatment and has 280 publications including 131 refereed articles, 23 invited chapters and 9 books. Dr. Birmingham's research has focused on nutrition and the brain, the effect of ambient temperature on anorexia nervosa and the medical management of eating disorders. He is focused now on LORETA imaging and neurofeedback of patients with disorder.

Rhonda Brown started her career as a lab-based researcher, developing an animal model for immune-mediated polyneuropathies during her Ph.D. and exploring the overlap between neurochemical, neuroendocrine and immune responses to stress and infective illness, including

bacterial translocation (i.e. leaky gut), during her post-doctoral fellowship. She works as an Associate Professor in the Research School of Psychology, Australian National University. She teaches health psychology and her research examines predictive relationships between stress, affective distress (e.g. anxiety, depression), sleep, fatigue, other symptoms, and illness outcomes in patients (e.g. cancer, overweight/obesity, sleep apnoea, multiple sclerosis) and community-well individuals. She also collaborates with other researchers to examine work-stress, burnout, communication performance and empathy in medical staff and medical and psychology students as well as immune function, fever response and infection in patients with anorexia nervosa. Over the past 20-years, she has worked extensively with each of the co-authors of this book.

Christopher J. Nolan is a clinician scientist and policy advisor in the field of diabetes and metabolic diseases. He recently stepped down as Director of Diabetes Services (2011–2018) and Director of Endocrinology (2016–2018) for ACT Health to take up a new position as Associate Dean of Research for the Medical School at the Australian National University. He is currently a Board Member of the Australian Diabetes Society (2018–) and an Associate Editor for *Diabetologia* (2016–). He directs an active diabetes research laboratory focusing on islet beta-cell failure in type 1 and 2 diabetes and the role of insulin hypersecretion in metabolic syndrome and related conditions. He is a lead investigator for the ANU Grand Challenges Project, Our Health in Our Hands, which includes research into improving the care of people with type 1 diabetes using a personalised medicine approach.

Einar Thorsteinsson works as Associate Professor at the University of New England, Australia. He worked on his Ph.D., the effects of social support on changes in cortisol and cardiovascular reactivity in response to stressful situations, at La Trobe University in Melbourne. He was awarded a Ph.D. in 1999 and then worked at La Trobe University in a fire fighting decision-making lab for two years before he moved back to focus on health psychology at the University of New England where he has built national and international research collaborations covering areas such as stress, social support, depression, anxiety, adolescent coping and health, and psychological well-being.

Yasmine Umar is a Doctoral Candidate at the Australian National University, extensively researching the predictors of disrupted sleep, obesity and affective distress in the general Australian population. She has also explored the relationships between stress, infection symptoms and chronic fatigue. She currently practises as a clinical psychologist, specialising in youth oncology.

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Comorbidity: What Is It and Why Is It Important?

Rhonda Brown and Einar Thorsteinsson

1.1 What Is Comorbidity?

Comorbidity refers to any distinct clinical entity that coexists with or occurs during the clinical course of another illness or condition [1]. In other words, it refers to the *co*-occurrence of two or more distinct illnesses, disorders or conditions in a single individual. As a result of the comorbidity, some disorders tend to occur together more often than they occur alone. For example, anxiety, depressed mood and impaired sleep often co-occur, and in this instance, the co-occurrence appears to be the rule rather than the exception [2].

In this book, the term *co-occurrence* is used to refer to the coexistence of multiple symptoms (or clinical signs), whereas comorbidity specifically

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refers to the coexistence of multiple illnesses, disorders or conditions. For simplicity, the terms illness, disease, disorder and condition will be used interchangeably, as appropriate to the medical or psychological literatures referenced in each chapter.

It is not possible to provide a comprehensive analysis of all comorbid disorders and concurrent symptoms in this book. Nonetheless, the book represents a significant step forward in its coverage of a broad range of concurrent disorders including overweight/obesity, diabetes mellitus type-II, cardiovascular disease, sleep-disordered breathing, impaired sleep/insomnia, disordered eating (e.g. binge-eating disorder), anxiety, depression, fatigue, anorexia nervosa and bulimia nervosa.

In contrast, prior published books on the topic have tended to examine a limited number of comorbidities, including that between anxiety and depression [3–10], depression and other disorders [3], comorbidity with rheumatic disease [11], epilepsy [12], hypertension [9] and lifetime (or non-concurrent) comorbidity [4]. However, Sartorius and colleagues [13] have comprehensively detailed the clinical challenges of managing medical illnesses (e.g. cardiovascular disease, cancer, infectious disease) that tend to co-occur with mental and behavioural disorders, including substance abuse, eating disorders and anxiety; they covered the clinical management of the comorbidities.

In this book, a focus of attention is the comorbidity between overweight/obesity (or proxy measures of it, e.g. high body mass index [BMI] or weight gain) and impaired sleep/insomnia, which is increasingly observed in clinical practice, but as yet is not fully understood. Specifically, overweight/obese individuals tend to take longer to fall asleep (i.e. longer sleep onset latency) [14], sleep for a shorter time [15, 16], and have poorer sleep quality [17], relative to non-obese controls (or lower BMI). However, little else is known about this common comorbidity, although the sleep problems do typically resolve once the person loses weight [18]. In Chapter 3, this comorbidity will be discussed in greater detail as will the links between the phenomena and certain behaviour, which may play a causal role in contributing to the disorders. In Chapter 2, existing theories that seek to explain the presence and/or development of comorbid symptoms and disorders will be discussed.

Additionally, in Chapter 4, comorbidity between overweight/obesity and diabetes mellitus type-II, sleep-disordered breathing (e.g. obstructive sleep apnoea [OSA]) and affective distress (e.g. anxiety, depression) will be discussed. In Chapter 6, the concurrence between anxiety, depression, insomnia/impaired sleep, fatigue, gut pathology and gut symptoms will be discussed. In Chapter 5, comorbidity between eating disorders (e.g. anorexia nervosa, bulimia nervosa) and sleep problems, anxiety, depression, gut problems and hyperactivity will be examined. In Chapter 7, symptoms/conditions (e.g. chronic pain, fatigue) that frequently co-occur with impaired sleep, psychopathology, and other co-occurring conditions will be briefly discussed, as will the potential role played by unhelpful behaviour, including sleep-disrupting behaviour.

Statistically, disease comorbidity is typically evidenced by high co-prevalence estimates between the different diagnoses; symptom concurrence is evidenced by moderate to high correlations between two or more composite measures (e.g. total construct scores), using validated questionnaires [19]. Consistent with this approach, the book chapters will provide detailed research evidence illustrating the degree of concurrence between the aforementioned disorders and symptoms, as appropriate to the specific chapter. Further, where possible, the emphasis will be on presenting meta-analytic and prospective longitudinal study results, rather than cross-sectional correlational results. That is to say, our current conception of causality typically requires that the cause of an event must *precede* its' onset in time. Only longitudinal (and experimental) study results can fulfil that criterion, to a greater or lesser degree.

However, appreciating the nature of the temporal relationship between two separate phenomena tells us little about the mechanism/s that underpin the relationship. As detailed in Chapter 2, there are few available theories to help guide the research on disease comorbidity, and as a result, we currently know little about the true nature of the phenomenon. Furthermore, a number of statistical and methodological (e.g. measurement) problems complicate our understanding of comorbidity, for example, by potentially inflating the extent of the observed relationship between the different phenomena. These methodological and statistical problems will be discussed in more detail in Chapter 8.

Finally, in Chapter 9, we will tie the threads together from the various chapters and reflect upon the most likely mechanism/s underpinning the development of comorbidity between the aforementioned disorders. In particular, we will discuss the likely role played by circadian rhythm *dys*function in the development of the disorders, along with the role played by sleep-disrupting behaviour and biological processes (e.g. elevated nocturnal body temperature). Finally, we will explore a broad range of novel, existing and repurposed therapy approaches that could show utility in treating the comorbid conditions.

1.2   Why Is Comorbidity Important?

In the twenty-first century, the tendency of patients to develop multiple disorders or conditions, rather than a single medical or psychological problem, is relatively high. For example, in a large study of 198,670 Spanish patients aged over 14 years [20], 42% had at least one chronic condition, and the prevalence estimate for comorbidity was one-quarter (24.5%) although the prevalence was higher in women (28.1%) than in men (19.4%), and it increased with advancing age until 69 years, when it stabilised. Of the 26 chronic health conditions surveyed, three distinct comorbidity burden patterns were detected, including high comorbidity (pattern B), intermediate comorbidity (patterns A and D) and low comorbidity (pattern C). Pattern B conditions included ischemic heart disease, congestive heart failure, cerebrovascular diseases and chronic renal failure, mostly in older patients (>70 years). Pattern A conditions included cardiac arrhythmias, hypertension (with/without complications), diabetes (with/without complications) and hyperlipidaemia, mostly in older patients. Pattern D included 14 conditions, for example, obesity, osteoporosis, dementia, and cancer, whereas pattern C included asthma, thyroid disease, anxiety, depression and schizophrenia, mostly in younger (<30 years) patients. Thus, several distinct comorbidity patterns were evident reflecting that different medical and psychological disorders tended to cluster together, in different general practice patients.

Similarly, high comorbidity prevalence estimates have been obtained in GP record-based studies in other countries. For example, a prevalence

estimate of 20% was obtained in an Australian study [21]; 29.7% had acute and/or chronic conditions in a sample from the Netherlands [22]; and 30% had comorbid illnesses in a Spanish population-based sample [23]. In the USA, about 25% of the population are reported to suffer from multiple chronic conditions and this percentage increases with advancing age [24]. Thus, it is evident that disease comorbidity is common in clinical practice and more broadly in the global community.

Comorbidity substantially increases the burden of illness in chronic illness patients. For example, the Global Burden of Disease Study [25] evaluated chronic and acute illness and injury burden on patients across 188 countries (1990–2013) using years lived with disability (YLD). Globally, from 1990 to 2013, disability rates were shown to rise, as people tended to live longer and experienced more illness. Additionally, comorbidity prevalence estimates rose substantially in absolute terms and also with increasing age; for example, the number of people with 10 or more disorders increased by 52% over that time. Further, in total, one-third of the participants had >5 chronic or acute illnesses, of whom 81% were <65 years of age [25]. Thus, it is evident that comorbidity occurs in younger as well as older individuals.

However, few studies have explicitly compared the degree to which different disorders are comorbid with each other, although higher comorbidity rates are reported in patients with heart (e.g. heart failure) and cerebrovascular conditions and lower rates are reported in patients with asthma and mental health conditions [21, 26, 27]. Nonetheless, depression is known to be a leading cause of Global Burden of Disease (GBD) based on years lived with disability (YLD) and disability-adjusted life years (DALYs); it may contribute to suicide and cardiovascular disease [28]. However, expanding this examination to cover other mental health problems including substance use/abuse and the combined effects of the disorders is required; as the conditions are leading causes of DALY and YLD worldwide [29]. Furthermore, as shown in a UK study, nearly one-half (46%) of people with a mental health problem also had a chronic physical health problem/s, whereas fewer (30%) people with a chronic physical condition also had a mental health problem [30], suggesting that mental ill-health is a common comorbid health problem which may have implications for physical health.

Taken together, it appears that comorbidity is present in at least one-quarter to one-third of the population, including in general practice patients. Furthermore, comorbidity prevalence estimates have significantly increased over time and they tend to increase with advancing age, as do disability prevalence estimates [31]. Thus, as the global population ages, the extent to which we will be affected by comorbid disease burden is expected to substantially rise, although a substantial proportion of younger people are also affected by comorbidities. Therefore, there is an urgent need to better understand the nature of disease comorbidity and its likely causation, so that effective multi-modal therapies can be developed (or re-purposed) to treat the individual patients who have multiple comorbid illnesses.

Comorbidity tends to be associated with impaired daily functioning and low health-related quality of life (QOL), including the physical and mental health components of QOL [23]. More broadly, chronic illness patients often experience severe and/or debilitating symptoms; will likely undertake fear-provoking, painful or otherwise demanding investigations and treatments; experience a high degree of uncertainty related to the condition/s and their treatment; and about one-quarter of them will go on to develop clinically significant psychological distress. Adherence may also be reduced due to such severe symptoms and painful and demanding treatments reducing the efficiency of treatment and increasing costs. Even without a psychological disorder, patients will still need to psychologically adjust to their illness, which will require them to regulate their thoughts, feelings and behaviour; acquire new skills to manage their psychological symptoms; adopt a new lifestyle of self-care; establish collaborative relationships with their healthcare team/s; and, even then, sub-clinical affective distress (e.g. anxiety, depression) may occur [32]. Nevertheless, the *impact* of multiple different comorbid disorders (e.g. disability) tends to be greater than for a single disorder, as are the costs associated with it (e.g. financial, personal), as discussed in detail below.

However, despite the high prevalence of comorbidity and its considerable impact on individual patients, most medical and psychological researchers have tended to focus on *single* disorders or conditions, rather than (or in addition to) disorders that coexist with them; irrespective of whether the subjects are medical patients, psychological clients or community-derived non-clinical samples. For example, researchers may

investigate the relationship between certain risk factors (e.g. physical inactivity) and depressed mood, without examining their relationship to other coexisting symptoms (e.g. impaired sleep, fatigue), despite the common propensity of depression to coexist with anxiety [33], impaired sleep [34] and fatigue [33, 35]. However, many researchers will at least statistically control for the potential effects of the concurrent symptoms. For example, they may assess the predictive relationship between risk factors and depressed mood, and partial out the effects of anxiety on the outcome measure, to obtain a purer estimate of the risk factor–depression relationship. Such an approach can assist researchers to better understand the extent to which particular risk factors and depressed mood are related, but this approach potentially ignores the possibility that anxiety is functionally related to depression via a number of possible mechanisms, as discussed in Chapter 6.

Additionally, *few theories of disease comorbidity* exist to help guide the comorbidity research. Specifically, as discussed in detail in Chapter 2, there are few available *clinical* theories with any utility in explaining the way in which different-but-related disorders and symptoms are likely to coexist and the mechanisms by which they will develop. Such a theoretical model would greatly assist researchers and clinicians to better understand the likely complex causal relationships that exist between different risk factors, medical illnesses and psychological disorders; it might also facilitate the evidence-based co-treatment of different comorbid disorders and conditions.

However, most existing *therapies* have not been designed to treat different-but-related disorders. Nor have they been examined for their utility in treating coexisting conditions. Similarly, clinical practice guidelines and disease management programs typically focus on single diseases but fail to take comorbidities into account; instead, they tend to deal with the disorders as if they are isolated clinical entities [36]. Thus, there is a clear need to update the clinical practice guidelines and patient management approaches to take disease comorbidity into account, especially in the case of highly comorbid disorders and conditions. Furthermore, there is a need to develop and evaluate novel (or repurposed) evidence-based therapies to more effectively treat the aforementioned comorbid conditions.

However, as discussed in Chapter 9, there appear to be few novel therapies on the horizon that might remedy the comorbidities; there is no clarity as to whether existing therapies could be used to concurrently treat comorbid illnesses or if a sequenced approach to therapy might work best. Nevertheless, there are a few notable exceptions: for instance, cognitive behavioural therapy (CBT) can effectively treat depressed mood, fatigue, insomnia/sleep problems and eating disorders; and there are disorder-specific variants of CBT to treat depression [37], fatigue [38], insomnia (CBT-I) [39] and eating disorders (CBT-E) [40]. However, the CBT protocols do not generally provide any detail about the way in which the comorbid disorders should be managed together, either concurrently or sequentially, in a single individual. Additionally, antidepressants have been used to treat sleep problems in patients with depressed mood, but the findings are typically mixed, with some studies showing that the drugs can improve insomnia [41], whereas others show the drugs may worsen insomnia [42]. Thus, there is a clear need to systematically review the efficacy of antidepressant use in treating insomnia. A Cochrane review that began in 2013 found that there was little evidence for the effectiveness of SSRIs in treating impaired sleep and any apparent improvements in sleep quality were short-lived, although the findings were only preliminary as insufficient studies could be sourced to examine this issue [43].

1.3   What Is the Cost of Comorbidity?

Disease comorbidity is associated with a range of economic, societal and personal costs. Economic costs can include the direct costs to the healthcare system of managing multiple health problems (e.g. prolonged recovery time); direct costs to other sectors (e.g. provision of social care); and, indirect costs such as the lost opportunity to contribute to economic productivity (e.g. reduced workforce participation or participation in school, etc.). The full *economic costs* of comorbidity are largely unknown, especially the estimates of the impact beyond the healthcare system; in this case, the estimates are mostly of indirect costs, including productivity losses due to under-employment resulting from absenteeism [44].

Nevertheless, it is broadly appreciated that the financial costs of managing two different chronic disease patients, one with diabetes and the other with heart disease, will be *higher* than the cost of managing a single patient with comorbid heart disease and diabetes [45]. This disparity is due to the need to duplicate certain aspects of services provision to each individual patient (e.g. administrative costs, clinic attendance), indicating that there are likely to be potential per capita cost savings associated with the treatment of patients with comorbidity. However, a single patient with comorbid illness may require additional health resources (e.g. more time with the doctor, longer hospital stay) and longer and more intense treatments, relative to two different patients with a single chronic condition. As detailed below, relatively few studies have compared the economic costs of managing multiple comorbid disorders with the uncomplicated presentation and treatment of single disorders.

However, the costs associated with managing comorbid mental health disorders (e.g. anxiety disorders, depressive illness) and related conditions (e.g., sleep problems) are known to be high. For example, at any one time, about 2% of the Australian population is reported to be affected by a serious mental health condition; in financial terms, this translates into an annual societal cost of AU$15 billion in Australia and NZ$3.1 billion in New Zealand [46]. However, the full costs of managing the separate conditions tend to be underestimated due to the omission of costs related to the patients' other comorbidities [47]. Further, a recent US study showed that if a patient was hospitalised for a *non*-mental health condition (i.e. heart failure), the cost was significantly higher if they had a comorbid mental health condition (e.g. depression); that is, the additional costs of depression ranged from US$1844 to US$7763 per patient per psychiatric diagnosis, and it likely resulted in a longer hospital stay [48]. Thus, despite the lack of specific research, it is evident that the financial costs of managing comorbid mental and physical health problems are high.

Similarly, sleep problems represent a significant cost to the individual and the wider community, including the cost of therapy and costs associated with work-related injuries, motor vehicle accidents and losses to productivity due to sleep disorders [49]. For example, in four US corporations, workers who had insomnia and/or insufficient sleep syndrome had significantly lower productivity, workplace performance and work safety

outcomes than those without a sleep disorder; the loss to productivity due to sleep problems was estimated at $1967 per employee annually [50]. Similarly, the costs linked to sleep problems in Australia are estimated to be about $5.1billion per annum, but again, the value excludes the costs of managing people's other comorbid conditions [49]. However, Deloitte Access Economics and the Australian Sleep Health Foundation computed the direct and indirect costs of several sleep disorders including insomnia, OSA and restless leg syndrome (RLS), using 2010 data [51]. The indirect costs of treating OSA included managing any comorbid hypertension, vascular disease, depression and related motor vehicle and workplace accidents. In total, the sleep disorders cost about AU$818 million which included sleep disorder treatment ($274 million), treatment of other disorders caused by the sleep problem ($544 million), and non-financial costs of the disorders, including lost productivity ($3.1 billion/year) [51], although some researchers have argued that the full costs were underestimated, due to the use of overly conservative prevalence estimates for OSA, RLS and insomnia [49].

Thus, it is apparent that the financial costs of managing comorbid illnesses are high. It is certainly higher than the cost of managing the uncomplicated presentation of a single disorder. However, relatively few studies have examined the direct and indirect costs of disease comorbidity. Nevertheless, the costs of comorbidity will likely vary depending on the type and extent of the comorbidities. For example, common disorders (e.g. insomnia, obesity) will tend to cost the most to manage, in terms of the total health sector costs. Similarly, conditions that tend to co-occur the most will tend to contribute more to the costs of managing other disorders; for example, sleep problems are more strongly linked to depressed mood than anxiety disorders; and [35, 52] thus, the costs of sleep-related comorbidity will tend to be greater in patients with depressed mood than in those with a comorbid anxiety disorder.

In contrast, chronic pain is more strongly linked to anxiety than depression, and so the economic costs of managing anxiety may be higher than the costs of managing depression in chronic pain patients. For example, nearly one-half (43.9%) of a sample of Spanish patients with chronic widespread pain reported anxiety and whereas only one-quarter (27%) reported depression [53]. Taken together, the results suggest that the costs

(and disability) associated with chronic widespread pain, which is often concurrent with anxiety, depression and sleep problems, is higher than the costs of managing matched control patients who do not have chronic widespread pain [53]. The specific costs associated with managing other comorbid disorders (e.g. diabetes mellitus type-II) will be described in greater detail in the relevant book chapters.

Disease comorbidity has been shown to be associated with *shorter life expectancy*. For example, the risk of myocardial infarction increases four—fivefold in the presence of depressive symptoms, even after controlling for medical factors [54]. Similarly, patients with comorbid depressed mood and overweight/obesity [55], diabetes [56, 57] and insomnia (i.e. sleep duration) [58] are more likely to experience an earlier than expected death. Depression comorbidity also increases the mortality risk in patients with high mortality illnesses such as OSA [59, 60] and anorexia nervosa [61], although there is a lack of research on OSA [62]. Similarly, the high mortality rate in schizophrenia patients has been shown to be at least partly attributable to comorbid cardiovascular disease and cancer [63]; a recent meta-analysis that evaluated studies from 25 countries confirmed this pattern, showing that the high mortality rates linked to schizophrenia were largely attributable to the presence of comorbid conditions [64].

Similarly, the Royal Australian and New Zealand College of Psychiatrists [46] reported that comorbidity of a mental and physical health condition reduced life expectancy in men and women. Patients with anxiety and/or depression were at greater risk of all-cause mortality and risk of death from specific illnesses, probably due to the ill-effects of the comorbid physical health condition/s (e.g. cardiovascular disease, diabetes) [65]. In addition, hospital inpatients with depressive symptoms are more likely to experience readmission or increased mortality risk, relative to patients without depressive symptoms [66]. Similarly, using data from the *US National Health Interview Survey* (1999–2011), Pederson and colleagues [66] showed that people with anxiety/depression were likely to die an average 7.9 years earlier and had a doubled mortality risk and risk of hospital readmission, relative to non-anxious and depressed controls [66]. Finally, in a study of >5 million US military veterans, of whom 850,000 were depressed, high baseline depression was linked to a 17% increased risk of all-cause mortality and specific increases in mortality due to heart disease, respiratory

illness, cerebrovascular disease, accidents, diabetes, nephritis, influenza, Alzheimer's disease, septicaemia, suicide, Parkinson's disease and hypertension [65]. Thus, it is evident that comorbidity between a mental health and physical health condition is linked to a shorter life expectancy. Specific details of the mechanisms that may underpin the elevated mortality risk in patients with comorbid illnesses will be discussed in greater detail in the relevant book chapters.

Comorbidity is also typically linked to substantial *disability*. Disability can limit a person's ability to function adequately in their current environment, either mentally or physically [67]; this can adversely impact upon multiple different aspects of their daily life. For example, a person with diabetic retinopathy may develop permanent vision impairment and this may interfere with their ability to perform daily domestic duties (e.g. cooking), care for children and/or do paid work, unless accommodations can be made in the workplace. Specifically, disabilities such as mobility and cognitive impairment often result in a change in the patients' work status, including withdrawal from work, reducing work hours and/or changing the type of work performed, for example, as seen in patients with multiple sclerosis [68]. Furthermore, disease comorbidity can limit a person's capacity for self-care [32], suggesting that patients with multiple comorbid disorders may struggle to manage the different illnesses and deal with the extent of their disabilities. According to 2012 figures, about 4.2 million Australians were affected by a disability, and compounding this issue, the unemployment rate was 9.4% among disabled individuals, compared to 4.9% in those who were not disabled [69]. Thus, disability is common in the community, although it is unclear just how much of this is related to comorbid disease burden.

In particular, comorbidity between mental and physical health conditions has been shown to more than double the odds that a person will suffer from severe disability [70]. Several large mental health surveys have shown that when mental health conditions are compared to physical health conditions, the mental health conditions are more likely to predict severe disability burden; specifically, the odds of experiencing a severe disability were greater (more than additive) in patients with a mental and physical health condition/s [70]. Further, comorbidity between psychological

disorders has consistently been shown to be related to poorer prognosis and greater therapeutic demands from patients [71]. Taken together, the results suggest that patients with comorbid health problems are more likely to experience disability, poorer prognosis, and have more complex health needs than patients with a single disorder, especially if they have a concurrent medical and psychological problem/s.

Importantly, disability is described as a societal phenomenon inasmuch as it is typically defined in terms of the extent to which it impairs a person's *engagement* with activities, including work, and the extent and nature of their social interactions [72]. Thus, the effects of disability will tend to extend beyond the individual to include their family unit, friends and social network, and its effects may change over time. For example, a patient may withdraw from their social network while they are unwell, but if their health improves, they may need to rebuild the network and/or make new friends or contacts. Alternately, a spouse may need to take over as the primary breadwinner or give up work to care for the patient, resulting in a loss of family income, financial stress and tension related to changes in family roles and responsibilities and the broader redefinition of social roles. Thus, it is apparent that comorbid disease burden has important implications for the broader community, including the possibility that the affected individual will prematurely withdraw from or reduce their engagement with important aspects of their world. For example, a person may need to withdraw from work and/or their social network due to disability, and additionally, they may become stigmatised because of the illness or the disability.

Stigma involves labelling an individual or group therefore setting them apart from others. In nations such as Australia, stigmatised groups typically include people who are disabled, Indigenous, LGBTQI, unemployed, homeless, poor, asylum seekers and those with mental health conditions. Stigma is known to potentially lead to health inequality [73]; the more a person (or population) is stigmatised, the more likely they are to suffer disadvantage, although it has not been examined in regard to comorbidity. Nevertheless, a review examining the mental health of Australian homeless youth has suggested that homelessness is linked to increased suicidal behaviour, the presence of psychiatric disorders and psychological distress [74].

Thus, it is apparent that comorbidity is associated with considerable *personal costs* to individual patients, including the physical and psychological impacts of the conditions. For example, they will likely experience multiple physical and/or psychological symptoms; need to undertake multiple different therapies, each of which may need to be taken at a different time of day or under different conditions (e.g. before meals); need to attend multiple different therapy appointments at different locations, at considerable personal cost; and need to work with multiple different health practitioners to co-manage their conditions. As a result, the burden of comorbidity and its treatment is likely to interfere with a patient's ability to lead a normal life, derive a sense of personal control and psychological well-being and maintain important social relationships and social roles (e.g. parent, worker). Furthermore, certain aspects of the illnesses (e.g. severity, disability, prognosis, treatment) may increase the likelihood that they will experience stress, affective distress (e.g. anxiety, depression), grief and possibly other comorbid conditions (e.g. sleep disorder).

In particular, patients with several different-but-related conditions may spend many hours seeing various healthcare professionals, each of whom will separately evaluate and treat the medical and psychological problems, in an uncoordinated way. For example, a patient with comorbid overweight/obesity, binge-eating disorder, diabetes mellitus type-II, OSA and depressed mood may variously be managed by an obesity clinic, endocrinologist, sleep apnoea clinic and clinical psychologist; they may separately participate in weight loss and exercise programs and be prescribed diabetes medication, continuous positive airway pressure (CPAP) therapy and cognitive behavioural therapy. As mentioned above, this uncoordinated approach to patient care can represent a substantial burden to individual patients and their families; for example, it may interfere with their capacity to earn a living or fulfil important social roles as well adding to the financial costs of caring for the patient.

Finally, as mentioned in Sect. 1.2, most healthcare services are currently ill-equipped to treat patients with multiple comorbid conditions [75]. In most clinical settings, patients tend to be prescribed a single treatment plan for each separate condition, rather than a single coordinated therapy plan for individual patients. Each treatment plans will typically be administered by a different medical team or allied health professional;

there is often little communication between the staff, and between healthcare workers and patients [76]. Similarly, in some poor countries, there is a lack of healthcare providers who have expertise in managing common comorbid illnesses (e.g. HIV/AIDS and tuberculosis) using an integrated treatment plan which takes into account the interactions between the different diseases [77]. Furthermore, where clinical practice guidelines exist for the treatment of comorbidities, they have typically been found to be less than adequate and may potentially increase the burden to patients [78].

Thus, it is clear that patients with substantial comorbid illness burden require an *integrated* therapy approach, which separately (and together) addresses each medical and psychological condition. For example, a patient could receive multiple co-therapies together or sequential therapies that are co-managed in individual patients, although few comorbidity therapy protocols currently exist. Nevertheless, multidisciplinary treatment approaches will likely have utility in optimally managing a person's comorbid illnesses, as they tend to permit the provision of coordinated evidence-based therapy, using co-therapy or sequential therapy protocols.

Multidisciplinary care typically involves patients attending a central location to see a number of medical and/or allied health staff involved in their care. Clinicians can communicate with each other about the precise sequencing of the prescribed evidence-based care and the management of the related problems (e.g. therapy side effects, affective distress). For example, a breast cancer patient may undergo surgery, chemotherapy and/or radiotherapy, as sequenced by the treatment team, using established sequential therapy protocols that minimise side effects and maximise the clinical response to therapy. Her psychological condition can also be managed in the same clinic by allied health staff in coordination with the medical team. Unfortunately, multidisciplinary care approaches have, for the most part, not been utilised in the treatment of comorbid illnesses, except in diabetes patients, who are sometimes managed in the multidisciplinary care setting; in which case, diabetes and comorbid conditions (e.g. depressed mood) can be concurrently treated, as discussed in Chapter 4.