

Impact of Depression on Treatment Adherence and Survival from Cancer

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There are cognitive, motivational and social mechanisms by which depression, even that which is not solely cancer-related, can diminish self-initiated health behaviour change and adherence to recommended cancer treatments. This non-adherence can potentially threaten a patient's health and healthcare outcomes, and could ultimately influence survival.

Poor mental health can be a barrier to treatment adherence by undermining the understanding and memory, motivation and attitudes, and social support resources that are all essential to achieving adherence. For treatment adherence levels to remain optimal, physicians and other healthcare professionals should carefully enquire about, and if necessary help the patient receive treatment for, symptoms and behaviours of depression.

THE RELATIONSHIP BETWEEN DEPRESSION AND SURVIVAL IN CANCER

A number of studies provide evidence of a relationship between depression and decreased rates of survival after a cancer diagnosis.

One study of breast cancer patients demonstrated that, at five-year follow-up, women with higher levels of depression had a significantly reduced likelihood of survival [1]. In another study following patients from several months to over 10 years after diagnosis, those with a sense of hopelessness/helplessness were found to have a significantly lower survival rate than those without [2]. In a population-based study of over 10 000 participants, cancer patients with depression had a significantly greater risk of death at eight-year follow-up than did those who were not depressed [3].

Although research to date has not specifically examined adherence to treatment as a mediator of the relationship between depression and cancer survival, non-adherence to treatment is likely to contribute to increased cancer morbidity and mortality [4] *and* non-adherence is higher when patients are depressed [5].

This chapter focuses on examining the relationship of depression to patient adherence in cancer treatment, and on explaining the mechanisms that may account for this relationship.

THE CONCEPT OF ADHERENCE IN CANCER TREATMENT

In the broadest sense, the term *adherence* refers to a patient's behavioural response to his or her health professional's recommendations for health and health care [6]. A patient may follow, or not, a clinician's recommendations to change health behaviour and/or to follow a protocol for disease management activities. Health professionals' recommendations can be for primary prevention, such as a low-cholesterol, low-fat diet, and regular exercise, for secondary prevention, including screening for disease, or for tertiary prevention to cure or manage disease progression (e.g. to slow or minimize damage). Disease management activities may include appointment-keeping for medical visits, self-care activities, and following medication schedules for a particular length of time at a specified dosage and frequency [7].

Failure to adhere to treatment is a common patient response in the context of serious illness such as cancer. Recently, meta-analytic work found that, in more serious diseases including cancer, patients who self-reported poorer health were at significantly greater risk of non-adherence than those who reported their health to be good [8]. This

finding was even stronger when patients' health status was assessed with objective measures of disease severity.

With less serious conditions (e.g. arthritis, cataracts), patients in poorer health were more likely to be adherent. However, in more serious diseases (such as cancer, heart failure, HIV), patients who were objectively more severely ill (i.e. had poorer health status as assessed by disease stage in cancer, ejection fraction in heart disease, or viral load in HIV), were *less* likely to be adherent to their regimens than those with better health status [8].

Poor treatment adherence may arise for a variety of reasons, including: a lack of full understanding of the meaning and importance of the regimen, having doubts about the efficacy of treatment, experiencing overwhelming side effects and suffering, and the physical and/or psychological demands of facing a serious illness such as cancer.

OUTCOMES AND CONSEQUENCES OF NON-ADHERENCE

Patients' adherence to clinicians' recommendations for health-promoting behaviours and disease treatment are essential for optimal health outcomes. Meta-analytic evidence shows that adherence is significantly correlated with better healthcare outcomes (with a combined effect size, unweighted mean $r=0.26$). So, there is a 26% difference in positive health outcomes achieved by those whose adherence is high versus those whose adherence is low [9]. The odds of a good health outcome are 2.88 times higher overall when patients are adherent. Across disease conditions and treatment regimens, however, there exists considerable variability in the relationship between outcomes and both adherence and health behaviours.

There are important consequences of non-adherence, which include poor symptom control, disease recurrence, and/or shortened survival time. Ending treatment early or failing to adhere properly can increase the risk of disease recurrence and metastasis [10]. For instance, patients undergoing breast conservation therapy and radiation have been found to have worse survival when they failed to adhere to their radiation protocols [11]. Other research has found that missing

appointments was a key predictor of shorter survival time from breast cancer [12], and research on stage III colon cancer has shown increased risk of mortality when patients fail to complete adjuvant chemotherapy [13].

Some standards of care in cancer suggest a required level of at least 80% adherence [14]. This threshold may be similar to that in HIV care, where patients who are more than 95% adherent to their protease inhibitor medication regimen have significantly better outcomes than those with lower rates of adherence [14]. Adherence below the threshold point might actually be dangerous to the patient, such as with the adjuvant therapy of tamoxifen for breast cancer, where greater patient benefits (decreased risk of recurrence) are proposed to occur only after five years of adherence to medication. Many women discontinue tamoxifen sooner, however, often for psychosocial reasons [15]. In the case of oral or intravenous chemotherapy, side effects that influence quality of life contribute to early cessation of medication-taking, and subsequent failure to derive therapeutic benefit [16].

In addition to directly affecting survival, non-adherence can erode trust in the physician-patient relationship, contributing to frustration for both parties. In addition, there are economic costs of unused prescriptions and unnecessary, unproductive, or wasted medical visits.

The relationship between adherence and outcomes is, of course, not perfect and it is not necessarily linear. Kravitz and Melnicow [17] suggested that the adherence and outcome relationship might be curvilinear. In cancer treatment, as in many conditions, it is possible that increasing diligence over health behaviours may contribute to healthier outcomes only to a point. The advantages of health behaviour may follow the threshold model, in which adherence to treatment such as medication, or self-initiated health behaviour change (e.g. regular exercise), may need to exceed a threshold in order to be effective. Once that threshold is reached, however, there may be marginal benefits and the worry and burden of adhering (e.g. food denial, exceptional vigilance for screening) may add so much stress to the patient's life as to reduce its quality.

Perfect adherence to a suboptimal or erroneous treatment may itself threaten health outcomes [18]. Following 'health recommendations' (e.g. some herbal products or alternative medicine 'cures' such as

Laetrile) from unreliable sources may be dangerous and/or substitute for effective treatments [19]. Some 'alternative' or 'complementary' methods can, of course, be quite effective (e.g. acupuncture for the management of chemotherapy symptoms [20]) while others may be used by patients who have abandoned evidence-based treatments [21].

Finally, adherence has a complex relationship to health because it is difficult to separate the benefits of treatment from the benefits of adhering. There is empirical evidence of a 'main effect' of adherence (even to placebo), such that adherence may be better than non-adherence regardless of what is being adhered to [22, 23]. The potential psychological states that underlie adherence and mediate its effects may be very powerful in their contribution to cancer outcomes.

RATES OF NON-ADHERENCE IN CANCER

Despite the central importance to survival and to healthcare outcomes of many health behaviours and medical treatments, more than 20% of cancer patients have been found to be non-adherent to a variety of treatments (including oral ambulatory chemotherapy, radiation and adjuvant therapy) [24]. Of course, the wide variety of treatment regimens in cancer care results in varying adherence rates. Rates of adherence to tamoxifen treatment for breast cancer have been found to range from 69 to 79% (focusing on adherence and persistence over five years of treatment) [25–27]. Adherence to adjuvant chemotherapy amongst lung cancer patients has been 84% for four of six cycles and 50% for all six cycles [28], but other findings suggest that only about 50% of patients follow through with all recommended cycles of chemotherapy for lung cancer [29]. One study of adjuvant chemotherapy treatment for colon cancer showed 78% adherence [13] and, amongst skin cancer patients, 84% of those who survived melanoma conducted self-examinations at least once a year, but only 59% wore sunscreen [30].

FACTORS AFFECTING ADHERENCE

Patient non-adherence to cancer treatments is multi-faceted. Intentional non-adherence in the context of cancer could reflect the patient's choice

not to continue treatment, with its attendant side effects, although it was prescribed in order to prevent recurrence and increase chances for survival. A patient might purposely miss follow-up appointments, or take partial doses of a regimen because he or she feels asymptomatic or does not understand or believe in the purpose of the treatment. Unintentional non-adherence can also occur because of some misunderstanding about the regimen (e.g. timing or dosing), forgetting to follow through because of a chaotic lifestyle, competing responsibilities, or a lack of necessary resources. Of course, the line between intentional and unintentional non-adherence may be a fine one, such as in cases of motivated forgetting or allocation of time and money resources to less important, but more pleasurable, activities than chemotherapy.

The Information-Motivation-Strategy Model[©] (IMS model[©]) [31] involves three broad categories of factors that can help to guide our subsequent analysis of the mechanisms by which depression can inhibit health behaviour change and treatment adherence in cancer. The IMS model[©] states broadly that in order to initiate or adhere to a health behaviour or treatment, patients must: (1) *be informed* (i.e. know what health behaviour or treatment they are expected to perform, and the reasons why); (2) *be motivated* (i.e. want to carry out the behaviour; are motivated by their beliefs, expectations, desires, attitudes and feelings), and (3) *strategize* or plan to carry out the behaviour (i.e. possess the emotional, financial, practical and social resources, including social support, necessary to translate the desired behaviour into action) [31, 32]. Many predictors of adherence have been identified in the empirical research literature and fall into these three broad groups of factors; this simple model provides a framework for understanding adherence to treatment succinctly. The IMS model[©] identifies the cognitive, motivational and resource-related factors that influence adherence, and can organize our analysis of adherence difficulties faced by cancer patients who are depressed.

HOW DEPRESSION CAN AFFECT ADHERENCE IN CANCER

Depression is very common in cancer. As many as one fourth of cancer patients suffer from major depression [33]; also, anxiety may occur

alone or in conjunction with depression [34]. Patients who suffer pain, declining physical status, and the need for ongoing active treatment have a significantly higher risk of depression [35].

The relationship between any patient's depression and non-adherence is strong and significant. In meta-analytic work, compared with non-depressed patients, the odds are three times greater that depressed patients will be non-adherent to their medical treatment recommendations. In the case of cancer, psychological, behavioural and biological pathways can be traced from serious illness stressors through the disease course to non-adherence, suggesting that the effects of depression on adherence can involve interactions amongst physiology, behaviour and emotional experience [36]. Depression can interfere with a patient's ability to adhere to medical regimens including both the desire and the ability to manage behaviour change that is vital when facing chronic conditions such as cancer. Major and minor depression alone can substantially impair quality of life and increase disability [37], and when depression is comorbid with other chronic conditions, quality of life can suffer considerably [38]. Depression can appreciably enhance cancer progression indirectly by jeopardizing adherence to essential cancer treatment regimens [33].

When patients are confronted with the challenges of diagnosis of a serious or life-threatening condition, long-term, health-related habits may be even more difficult than usual to change. Patients' patterns of self-initiated, health-promoting behaviours, such as dietary changes and exercise, may be jeopardized by the stress of complex treatment regimens [8, 39]. Social system factors, environmental factors, and coping patterns may combine with new or existing depression to prevent the adoption of health promotion and disease prevention activities and threaten adherence to treatment. Adherence behaviours can become increasingly difficult with deteriorating health [40]. Patients may find themselves doubting the efficacy of treatment, and they may find their interactions with providers becoming more strained as they face treatment frustrations or grow more severely ill [41, 42]. Adherence to treatment may even seem futile, and patients may become more depressed, socially withdrawn, and hopeless (or even ambivalent) about surviving [43]. When patients struggle with serious medical conditions, depression can contribute to many factors that are essential to initiating and

Table 5.1 Ways by which depression affects adherence to anti-cancer treatments

Inability to integrate cancer diagnosis and treatment information
Reduced motivation towards self-care; difficulty planning
Negative health beliefs and pessimism about treatment
Avoidance of health-promoting behaviours
Social isolation and withdrawal
Reduced use of community resources
Greater difficulty tolerating treatment side effects
Lack of desire and difficulty cooperating with plans for treatment

maintaining health behaviours, as well as processing and acting upon treatment recommendations [44].

The mechanisms by which depression affects adherence, and possibilities for clinical intervention to improve adherence, can be understood within the IMS model[©] (Table 5.1). Depression can interfere with the three categories of factors – cognitive, motivational and resource-related – that are essential for adherence. As stated, important pathways influencing adherence are: (a) patients' knowledge and understanding about their health, illness conditions, and treatments; (b) patients' self-perceptions and beliefs, desire and motivation to adhere; and (c) the resources and social support that are essential to make adherence and health behaviour possible. Depression that accompanies cancer can diminish patients' willingness and ability to adhere to their treatments and to initiate and maintain lifestyle changes [45]. This impairment can ultimately threaten patients' quality of life, health outcomes, and even survival. Working clinically to address these three elements of care, while also treating patients' depression, is essential to limit the potential compromise of care. Here we offer both empirical clinical research and theoretical argument to support the use of the IMS model[©] of adherence to care for cancer patients with comorbid depression.

Depression and Cognitive Processes: Effects on Information

A primary determinant of adherence is the patient's knowledge and understanding of the treatment. In cancer care, patients typically must

integrate a great deal of information about their disease and treatment interventions, including not only their diagnoses and the reasons for various treatment choices, but also the treatment regimens including medication scheduling, dietary restrictions, and self-care activities, as well as how to cope with side effects and schedules for monitoring and follow-up. Under the best of circumstances, many patients forget what they have been told by their physicians; one study found that patients forgot 50% of what they were told by the time they exited the medical visit [46].

Low socio-economic status and health literacy are serious risk factors for non-adherence. A study of impoverished early stage breast cancer patients being treated with radiation therapy found that only 36% of patients were fully adherent, and predictors of non-adherence that approached traditional significance levels included patients' literacy [11]. When patients are emotionally distressed, the chances of forgetting are significantly increased [47]. A study focused on understanding information-seeking in end-stage cancer found that, when confronted with terminal illness, a patient's motivation to seek information about his/her condition could not be taken for granted and depended upon several factors: patient open-mindedness, medical facts, healthcare professionals' attitudes toward their patients' informational needs, and the hospital social environment [48].

Depression can seriously challenge the *cognitive functioning and information processing* essential for understanding treatments and organizing behaviour. Essential information (such as the reasons for and scheduling of various treatments, and requirements of self-care) may come from many sources, including health professionals, written instructional materials, and the input of family members. Depression and related stress, anxiety and even anger can impair the ability to learn and maintain new behaviours [49] or to undertake complex tasks that require planning and execution [50]. The physical and psychological symptoms that can interfere with mood, such as insomnia, lower energy, functional impairment, and 'vegetative' symptoms, can be confused with or contribute to depression. When patients are distraught over the course of their illness, they may be more likely to forget recommendations, and less likely to ask questions and participate in the medical visit [5, 38, 51]. Lower levels of patient participation are linked to poorer health outcomes [52]. Amongst

advanced cancer patients, for example, depression and anxiety contribute to physical, social, emotional and cognitive functioning impairments [47]. Even after controlling for the effects of pain and illness severity, anxiety and depression are independently associated with cognitive functioning and fatigue amongst cancer patients [53].

Depression and the Motivation to Adhere

Depression is characterized by pessimism about the future and about the self, which can interfere with health behaviour and adherence [5, 54]. Commitment to behavioural change requires patient motivation built on beliefs that support adherence. Depression can significantly undermine those beliefs, and can threaten motivation to follow recommended treatments. The Health Belief Model, for example, predicts that health behaviour change will occur if a person feels susceptible to a severe condition, and believes that adhering has more benefits than costs [55]. Depression can contribute to the belief that adherence is not worth the trouble associated with it [56]. Depression can also lead to diminished self-perceptions and limitations in personal self-efficacy, which are essential to behavioural commitment; patients with more confidence in their abilities to discuss their treatment with their healthcare providers are more adherent [57]. Moreover, depression can amplify somatic symptoms, causing additional functional disability and further reducing patient motivation to change behaviour.

Motivation is essential for the achievement of adherence, and patients' beliefs, attitudes and perceptions are central to their motivation. The discontinuation of tamoxifen is associated with beliefs that the risks of treatment outweigh the benefits [26, 56]. Patients who cope with the challenges of illness in a proactive manner, such as by seeking support and information, actively solving problems, and expressing concerns, may be more motivated to adhere than those who avoid the challenges of the illness and treatment [58].

Following cancer diagnosis, patients (typically those who are not depressed) may be strongly motivated to engage in behaviours driven by their health beliefs and attitudes about the effects of health behaviour on disease outcomes. Many initiate stress management,

quit smoking, begin aerobic exercise, and make major dietary changes [59, 60]; for instance, one study showed as many as half of current smokers quit smoking after a cancer diagnosis [61]. The concept of 'teachable moments' has been used to explain how, after experiencing health events such as serious illness, people are motivated to take on health-promoting behaviours [62]. People may engage in exercise, for example, to deal with the physical and emotional effects of cancer. Comorbid depression, however, can carry a substantial illness burden, often generating additional somatic problems such as fatigue, lowered quality of life, impaired social functioning, and disability [63]. Chronic illness can bring about guilt, worry, anger, sadness, confusion and fear [64]. Amongst cancer sufferers and survivors, anxiety, mood disturbance, fear of recurrence, hopelessness, concern for the effects on loved ones, and altered self-image are common, especially amongst those who are depressed [10, 65, 66].

Optimism and positive coping, in short supply when people are depressed, have been explored extensively as mechanisms through which ill individuals can become more emotionally resilient, motivated and better able to cope with cancer. Folkman and Greer [67] identified those who possess a 'fighting spirit', adopting an optimistic attitude and preferring to be well informed and active in decision-making. For cancer patients, optimism predicts improved quality of life, functional status, and the effective management of pain [68]. In general, characteristics such as optimism, hope and positive coping can directly facilitate positive mood and improved physical health through treatment adherence [69]. Development of a 'chaos narrative of illness', involving a story of disorder, distortion and fragmentation, can foster a sense of anguish, threat and feelings of uncontrollability [70]. Depression can contribute to maladaptive physiological effects throughout the disease course, raising both the symptom severity and corresponding treatment complexity, as well as jeopardizing the patient's belief in the efficacy of the regimen.

Depressed individuals who are chronically ill can resort to an avoidant style of coping, limiting their motivation to change. Avoidant coping involves denial, emotional instability, disavowal about the reality of the illness, and other immature defences. As a result, they may fail to adopt necessary healthy behaviours (healthy diet, exercise, adherence to treatment) and incorporate others that are dangerous to

health (e.g. smoking, abusing alcohol, abusing psychotropic medications). While problem-focused coping involves taking the steps necessary to influence the disease process, avoidant coping can severely interfere [71]. An approach-oriented style of coping, which involves seeking information and social support, positive reframing, problem solving, and emotional expression, can bolster adjustment to chronic illness [58]. Avoidance is often termed 'harmful coping' because problems are not faced and solutions are not found, contributing to non-adherence [72]. Improving patients' coping strategies, thus, can be effective in reducing symptoms of psychological distress that hinder health behaviour and the management of illness [73].

Depression and Limitations in Strategizing to Achieve Adherence

Living with cancer often involves coping with complex self-management regimens, and with the physical and emotional distress, social isolation, and threats to identity that accompany the illness. These challenges can strongly affect adherence and health behaviour [74]. Treatment of the cancer can be intimidating and require significant effort in managing side effects. Meta-analytic work [8] demonstrates that when patients have cancer, those in worse health are less likely to be adherent than those whose health is better. When patients are severely ill, their efforts at adherence and health behaviour can be easily derailed by the many physical, psychological and practical challenges that accompany illness [39].

Serious illness can interfere with obtaining and taking advantage of necessary resources (e.g. finances, time and access to care). Research in breast cancer, for example, suggests that patients may miss appointments for reasons including work commitments and poor transportation options [12]. Adherence and health behaviour depend significantly upon having the physical and social resources necessary to implement desired health actions. A patient's ability to purchase and prepare healthy food, to allocate time and financial resources to exercise, and to obtain transportation to medical services and treatments are examples of essential resource-related determinants of health. The acquisition and maintenance of resources can be severely

threatened by depression, which can interfere with mobilization of energy and resources [75].

Patients who possess less tangible emotional support and have less cohesive families are at greater risk of non-adherence [76]. Greater social support is associated with better adherence to both breast cancer screening [77] and chemotherapy for colon cancer [13]. Depression can lead to significant social isolation, and can threaten social connections that are essential to health, limiting practical support and preventing the use of available resources. The biobehavioural model offers suggestions for potential causal pathways leading from cancer stressors through disease course [10] and argues that the interrelationships between social support and behavioural and biological factors may affect adherence to treatment in acute and chronic medical conditions [78]. Depression can foster withdrawal and a sense of isolation from family and other sources of social support and can prevent an individual from seeking and utilizing resources (such as family assistance with medications and transportation to medical visits). Major depressive disorder, for instance, is associated with decrements in functioning, greater risk of marital distress and missed work, and accompanying threats to resources [79]. Both depression and cancer can foster social rejection and isolation leading to worsening depression and direct threats to adherence [80]. The cumulative experience of illness, depression, family conflict and financial burden may deprive an individual of the capacity to change and adhere to medical recommendations. Amongst older adults with depression, perceptions of stigma can predict medication discontinuation [81].

Finally, it is important that adherence not be unduly difficult for the patient; treatment must fit into the patient's lifestyle if it is to be successful. Adherence is compromised when the regimen is complex or side effects burdensome [57]. In chemotherapy, side effects that harm physical, social and emotional functioning (for example, in breast cancer, hot flushes and joint pain from adjuvant therapy [82]) can contribute to discontinuing the regimen before it has been completed, leading to the failure to achieve optimum benefits [16]. Radiation therapy can be physically and emotionally draining and accompanied by distressing side effects. Chemotherapy can compromise immune functioning, resulting in fatigue as well as the need for social isolation to reduce the risk of infection. The addition of

distressing side effects to existing depression can increase the chances of non-adherence.

CLINICAL RECOMMENDATIONS

It is critically important that physicians are aware of how depression in patients with cancer can affect their adherence. Patients should be screened for mental health problems, so that these challenges can be addressed in tandem with guidelines and recommendations for treatment adherence and health behaviour change. A number of specific recommendations for clinical practitioners follow.

First, patients should be helped to adhere by being assisted with the three major components of adherence: information, motivation and strategy. Adherence itself (even to placebo) can have positive effects on health and may provide some clues to the role of psychological states and the effects of cognitive, motivational and resource factors (including social support) to achieve treatment goals. The stress of diagnosis and treatment can affect the most basic aspects of patients' lives, including what they eat, how well they sleep, the degree to which they want to exercise, and their use of substances such as alcohol and tobacco. Adherence to clinicians' recommendations and patients' own self-directed health behaviours may be mutually reinforcing such that adherent patients may take on additional positive health behaviour changes. Their resulting positive expectations may increase their likelihood of further engagement in the care plan [83]. Non-adherent patients, on the other hand, may become defensive as they are further distanced from health information and their physicians, and they may move further away from health-promoting lifestyles [10]. More favourable outcomes can occur because adherent patients benefit from the direct therapeutic effects of their treatments, or possibly also because of the 'non-specific' effects of adhering [23, 84]. Benefits may accrue through biological, pharmacological, psychological and behavioural mechanisms, including optimistic expectations [22].

Second, non-adherence should be viewed as a potential clinical marker for depression. Physicians need to be aware of the strong relationship between non-adherence and depression, and when they recognize that patients are non-adherent, they should screen for

depression. Depressed patients should be referred for further mental health interventions. Physicians should follow-up to be sure that these patients receive appropriate treatment for their depression and should assess whether their adherence improves as a result.

Third, providers should foster a strong clinician-patient relationship, effective communication, and partnership. Building the therapeutic relationship will help providers to diagnose and effectively manage both depression and adherence. One of the most important steps to achieving adherence involves the development of rapport through the sharing of goals and hoped-for outcomes. When a patient is motivated to adhere to treatment recommendations, it is ideally (but by no means usually) the case that these choices are mutually decided upon by patients and their physicians through shared decision-making [85]. Demonstrating empathy for patients involves the provider's awareness of the perspective of the patient, understanding the patient's point of view, and communicating that perception to the patient. Such empathic behaviour should extend toward understanding the difficulties of disease management and medication-taking, and should view solving the challenges of adherence from the patient's perspective. By focusing on the patient's experience of and psychological response to illness, patient-centred care helps avoid fragmented care.

Communication is also essential to supporting patients emotionally and helping them find meaning in the illness, helping to balance its negative consequences and improving their adjustment [67]. Individuals who find meaning in their experience may feel a greater sense of control, improved psychological adjustment, better coping, mood and health status [69, 86]. Although research on finding meaning and adherence has not been done on cancer patients, research on patients with tuberculosis and HIV has indicated a significant relationship between assessment of meaning or benefit in life and adherence to treatment [87, 88].

Physicians can also communicate support for patients' positive expectations. The avoidance of pessimism and nurturance of hope promote better health behaviours and greater patient adherence to treatment through increased motivation. Research by Epstein [84] and others [23] suggests that the benefits of adherence occur regardless of whether treatment is an active medication or placebo; in experi-

mental studies, adherence to placebo resulted in lower mortality risk [89]. With new health habits comes greater confidence and a 'self-fulfilling prophecy' may ensue, in which patients' expectations alone drive beneficial outcomes. Self-efficacy expectancies of personal competence, optimism and a sense of well-being may lead to more adaptive physiological and immunological responses. In patients with cardiovascular disease, for example, these self-efficacy expectancies have been shown to play a vital role in persuading patients that they are capable of making healthier dietary choices [90].

Finally, whenever we examine health behaviour change and treatment adherence, we recognize that causal inferences are problematic because patient adherence and health behaviour can be both the cause, and the consequence, of psychological states. Patients might behave in healthy ways because they feel positive and hopeful, or they may feel positive and hopeful because they are behaving in healthy ways; those who are less distressed emotionally may be more likely to adhere, but it is possible that adherence, emotional experience, and health are all caused by another factor entirely (for example, the availability of specific social and financial resources; or individual characteristics such as expectations, locus of control, hardiness and optimism). It is not possible to do a controlled experiment, treating one group to emotional distress and determining its effect. In all research such as this, where randomized experiments and clinical trials are not possible, careful examination of potential conceptual, measurement and methodology artifacts is essential. Meta-analysis can provide one way of systematically examining research on these complex relationships, while also taking into account various methodological, measurement and substantive moderators [91].

It is possible to design interventions that relieve psychological distress amongst patients with cancer, and determine the resultant effects on adherence. In one study of patients with breast cancer, for example, treatment with selective serotonin reuptake inhibitors (SSRIs) resulted in improvements in depression, reduced perceptions of illness severity, and improvement in quality of life [92] (although adherence was not measured as an outcome). Another group therapy intervention for women with advanced breast cancer both ameliorated and prevented depression while promoting adherence to anti-cancer treatments [93, 94]. Interventions to increase patient self-efficacy have

been found to significantly improve adherence to pharmacotherapy and resulting depression outcomes [91, 95].

Ideally, further research will identify both mediating and moderating mechanisms in the process of improving health behaviour change and adherence. In the meantime, the IMS model[©] provides a conceptual framework to guide physicians and other healthcare providers in understanding patient barriers and facilitators to adherence, recognizing the central role played by depression and the need to manage and treat this important comorbid condition.

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