# COMPARING EXERCISE AND PRESCRIPTION MEDICATION AS THERAPY IN FIVE DIFFERENT CHRONIC DISEASES

by

JESSLYN LENA GRACE HODGE

B.Kin., The University of British Columbia, 2012

A MAJOR GRADUATING PAPER SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF KINESIOLOGY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Kinesiology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2017

## INTRODUCTION

Chronic diseases are among the most common and preventable of all health problems. Seven of the top 10 causes of death in 2010 were from chronic diseases[1] and the incidence rates are increasing each year[2]. Out of every 5 Canadian adults, 3 have a chronic disease and 4 are at risk of developing a chronic condition[3].

Treatment of chronic illnesses commonly includes long-term pharmacotherapy. However, adverse effects of drugs can cause some patients to be worse off than from the condition itself. A review of self-reported barriers to medication adherence among chronically ill individuals consistently reported that insufficient adherence to medication was induced by various medication side-effects[4], such as patients with high blood pressure taking antihypertensive medication[5]. Physical inactivity is a primary cause of most chronic diseases[6] and is a modifiable risk factor. Yet, the vast majority of Canadians do not meet recommended levels of physical activity with 9 out of 10 children and youth, and 8 out of 10 adults not meeting the Canadian Physical Activity Guidelines[7]. It is well-established that regular physical activity can reduce the chance of developing various chronic diseases and conditions[2,6,8,9].

The purpose of this review is to evaluate the literature and compare the impact of prescription medication and exercise on the development and management of five different chronic diseases: hypertension, type 2 diabetes mellitus, osteoporosis, depression, and breast cancer.

## HYPERTENSION

### Background

Hypertension (HTN) is one of the leading causes of disability and premature deaths worldwide[10]. Approximately one-third (85.7 million) of Americans ≥20 years old have HTN and the prevalence rate increases with age[11]. According to the American Heart Association, HTN is defined as a systolic pressure (SBP) ≥140 mmHg or a diastolic pressure (DBP) ≥90 mmHg[11]. Manifestations of untreated high blood pressure include myocardial infarction, heart failure, stroke, coronary artery disease, kidney failure, atrial fibrillation, peripheral artery diseases, damage to eye blood vessels, and sexual dysfunction[12,13]. The elimination of HTN could reduce cardiovascular disease mortality by 30.4% among males and 38.0% among females[11].

### Evidence-Based Medications

When clinically indicated, HTN patients will typically receive monotherapy or combination therapy from four classes of medication: angiotensin-receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEIs), β-blockers, thiazide diuretics, or calcium-channel blockers (CCBs). Data from 1999 to 2012 show that the use of various classes of antihypertensive treatment has increased substantially among people ≥20 years of age[14]. During this period, the use of ACEIs increased from 6.3% of the U.S. population to 12%, ARBs from 2.1% to 5.8%, β-blockers from 6% to 11%, and thiazide diuretics from 5.6% to 9.4%. The use of CCBs remained the same, at 6%. Typically, combination therapy would include combined agents from the following pharmacological classes: diuretics and β-blockers, diuretics and ACEIs, diuretics and ARBs, and CCBs and ACEIs[15,16].

*ACEIs*

In the renin-angiotensin system, angiotensin II is the main end-product when angiotensin I is cleaved by angiotensin converting enzyme, which ultimately leads to vasoconstriction and increased blood pressure[17]. ACEIs are vasodilators used to relax blood vessels and lower blood pressure by inhibiting ACE from forming angiotensin II[18]. Blocking angiotensin II formation subsequently suppresses aldosterone and promotes renal excretion of sodium and water, which in turn reduces blood volume, venous pressure, and arterial pressure. ACEIs downregulate sympathetic adrenergic activity by preventing the facilitating effects of angiotensin II on sympathetic nerve release and reuptake of norepinephrine. Additionally, these drugs inhibit the breakdown of bradykinin, an inflammatory mediator and vasodilator[19]. A Cochrane Review[20] investigating 92 trials and a total of 12,954 HTN patients found that when subjects took half to maximum their recommended dose of ACEI, the blood pressure lowering efficacy of the drug was -8/-5 mmHg.

*ARBs*

Angiotensin II binds to angiotensin II type 1 receptor, which mediates the pathways that lead to vasoconstriction and water retention, increases in renal tubular sodium reabsorption, and increases secretion of vasopressin and aldosterone, among other actions[17].Similar to ACEIs, ARBs are therapeutic inhibitors of the renin-angiotensin system. ARBs prevent the activation of the angiotensin II type 1 receptor by angiotensin II, thereby decreasing vasoconstriction and reducing blood pressure[21]. Combining 46 large-scale randomized controlled trials (RCTs), Heran et al.[22] found ARBs, on average, lowered participants' blood pressure by -8/-5 mmHg.

*β-blockers*

β-blockers are among the oldest and most commonly used antihypertensive medications available[23]. While also indicated for numerous other cardiovascular diseases (CVDs), β-blockers antagonize the effects of sympathetic nerve stimulation at β-andrenoceptors widely distributed throughout body systems. $\beta_1$-receptors are predominant in the heart and kidney and have several proposed mechanisms of action[24,25] that play a role in reducing blood pressure: reducing renin-angiotensin-aldosterone activity by preventing renin release; inhibiting the effects of norepinephrine; decreasing cardiac contractility; and decreasing sympathetic activity through monitoring neurotransmitter release. β-blockers blood pressure lowering efficacy has been found to range from -5 to -10/ -4 to -8 mmHg[24].

*Thiazide Diuretics*

Thiazide diuretics act on the nephron mainly at the proximal part of the distal tubule of the kidney[26]. These drugs block sodium chloride transport, resulting in sodium excretion and urine volume increases, which in turn reduce blood volume and pressure[18]. Although still not a fully elucidated mechanism, researchers believe changes in cardiac output and extracellular fluid volume are transient and, in the long-term, the major hemodynamic effect is a reduction in peripheral resistance due to subtle alterations in the contractile responses of vascular smooth muscle[27]. The American Medical Association recommends thiazide-type diuretics as initial therapy for most patients without convincing indication for another class[28]. A recent review of 60 RCTs found thiazide diuretic monotherapy to reduce HTN in patients by -9.1/-3.3 mmHg[29].

*CCBs*

CCBs promote vasodilation by reducing calcium influx into vascular smooth muscle cells through interfering with L-type voltage-dependent calcium channels in the cell membrane[30]. The blockage of calcium causes vascular smooth muscle to relax, resulting in the lowering of blood pressure. In cardiac tissues, CCBs have a negative inotropic effect (decrease force generation), negative chronotropic effect (decrease heart rate) and negative dromotropic effect (decrease conduction velocity), particularly at the atrioventricular node, all playing a role in vasodilator activity[18,30,31]. While both dihydropyridine and non-dihydropyridine CCBs are available treatments, dihydropyridines are more commonly used to treat HTN due to their greater vasodilatory effect[15,32]. A systematic review of close to 14,000 HTN subjects found a maximal blood pressure reduction of -10/-7 mmHg for dihydropyridines[33].

*Combination therapy*

HTN medication used in combination therapy should have complementary mechanisms of action, leading to an additive blood pressure lowering effect and improvement in overall tolerability. Law[34] investigated the effects of two different HTN drugs on blood pressure separately and in combination, using thiazides, β-blockers, ACEIs, ARBs, and CCBs at a fixed dose. Average fall in blood pressure was -7.0/-4.1 mmHg for the first drug alone and -13.3/-7.3 mmHg after adding the second drug when used at half the standard dose.

The American Journal of Medicine published a study[35] that quantified the effect of combining antihypertensive drugs from any two classes of thiazides, β-blockers, ACEIs, and CCBs. Using a thiazide alone, the mean placebo subtracted reductions in SBP was -7.3 mmHg and -14.6 mmHg when combined with a drug from another class. Reductions using other drugs alone

and in combination were -6.8 mmHg and -13.9 mmHg with ACEIs, -8.4 mmHg and -14.3 mmHg with CCBs, and -9.3 mmHg and -18.9 mmHg with β-blockers. A more recent article stated blood pressure lowering efficacy of β-blockers as a second-line therapy in primary HTN was not as substantial, at -6/-4 mmHg[36].

## Adverse Effects to Medications

### *ACEIs*

Dry cough has been shown to occur in up to 39% of cases of HTN patients prescribed ACEI drugs[19,37,38]. While this is a relatively common adverse effect, the rate of withdrawal in patients due to this symptom is reported on the drug label to have an incidence rate of only 1.3%[39]. However, Bangalore and colleagues[39] have uncovered a 31-fold greater incidence over recent years from numerous RCTs. This side effect is likely due to the bradykinin response, which also may be a contributor to other ACEI-induced negative symptoms including severe angioedema of the upper airways and death due to asphyxiation, and those incidence rates have been increasing over the last couple decades[19,40,41]. Several trials involving ACEIs were found not to report any adverse effects by authors, yet most of those studies were noted as being funded by drug companies that manufacture ACEIs[20].

### *ARBs*

Headache, upper respiratory tract infections, and influenza-like symptoms were among the most commonly reported side-effects based on data from a number of studies[40]. Postural dizziness is reported more often with ARBs than placebo[21]. Hypokalemia can occur in patients with impaired renal handling of potassium, but does not seem to require drug discontinuation.

A 2010 meta-analysis[42] showed likelihood of ARBs increasing the risk of malignancy. Bangalore[39] also reported chance of increased cancer risk with ARB and ACEI combination therapy, although not with use of ARBs alone. Contrary to these findings, two further meta-analyses[43,44] showed opposite results with no association between risk of new cancer and with ARB therapy in HTN patients. Mixed outcomes from many trials cause this topic to remain under debate.

*β-blockers*

As an increasing number of side-effects to β-blockers are being uncovered, this drug remains under continued scrutiny. A study investigating the association of β-blockers with depressive symptoms, fatigue, and sexual dysfunction reported no significant increased risk of depressive symptoms and only small increased risk of fatigue and sexual dysfunction[45]. However, a closer look at the data by fellow researchers raised several concerns, as it showed a 3-fold increase risk of withdrawal due to fatigue, and a 5-fold increased risk of withdrawal due to sexual dysfunction. This allowed Messerli et al.[46] to calculate that for every stroke or heart attack prevented, 3 patients were made impotent by β-blockers, and 8 experienced fatigue to the extent that they withdrew from such therapy, which they believe is not an acceptable risk/benefit ratio for a completely asymptomatic disease such as mild HTN. Alternate studies report even higher incidences of withdrawal in patients on β-blockers compared to other HTN medications, stating that overall it is not well-tolerated and has miserable compliance rates[47,48].

In a study of 102 hypertensive patients, of those on β-blockers as opposed to a different class of anti-hypertensives 32% reported an adverse effect of an absence of peripheral pulses and 41% of Raynaud's phenomenon[49]. A meta-analysis found an incidence of Reynaud's phenomenon to be 14.7%[50]. Additional common side-effects reported in other literature included headache,

dizziness, sleep disturbances, increased insulin resistance, dyslipidemia, new onset diabetes, and weight gain[48,51,52].

*Thiazide diuretics*

The British Hypertension Society[26] lists hypokalemia, hyperuricemia, hyperglycemia, hypercalcemia, and erectile dysfunction as adverse effects to thiazide diuretics. Many of these biochemical abnormalities can occur in a dose-dependent manner with diuretic therapy[53]. Compared to placebo group, the relative risk of withdrawal from clinical trial due to an adverse thiazide effect was 4.5 for high-dose regimens and 2.4 for low-dose regimens[54]. In the ALLHAT and SHEP studies, rates of hypokalemia seen with low-dose thiazide diuretic were 8.5% at 4 years and 7.2% at 1 year[55].

*CCBs*

Side effects due to CCBs include headache and flushing due to peripheral vasodilation, tachycardia, swelling of ankles, gum swelling, edema, dizziness, fatigue, constipation, diarrhea, nausea, rash, and drowsiness[5,30,31,56]. Chrysant et al.[56] found edema to be the most common adverse effect to CCB medication, occurring in almost 20% of patients. Subjects from another study had symptoms of peripheral edema progressively increase with duration of CCB therapy up to 6 months causing more than 5% to discontinue the medication[57]. Although, when used in combination with ARBs incidences of edema associated with CCBs decreased[56].

A case-control study showed that women aged 55 to 74 years taking CCBs for more than or equal to 10 years were associated with more than a 2-fold increased risk of invasive ductal and lobular breast carcinoma[58]. This relationship did not vary significantly by type of CCB used. While other studies have shown mixed results, researchers suggest interpreting this medication with

caution, but also encourage additional examining of the associations between CCBs and breast cancer risk[59].

*Combination therapy*

Particular combinations of HTN drugs are not recommended, such as dual renin-angiotensin-aldosterone system inhibition due to risk of hyperkalemia[60,61]. β-blockers and diuretic combinations have also been discouraged in patients with metabolic syndrome or prediabetes due to their increased risk for new onset diabetes[62]. This combination is also known to have erectile dysfunction side effects[63].

A study of approximately 85,000 patients found that adherence was inversely related to the number of medications prescribed. Anti-HTN adherence levels were 77.2%, 69.7%, 62.9%, and 55% in subjects receiving one-, two-, three-, or four-drug regimens[64]. More dramatic drops in adherence with increasing number of doses is seen with other studies[65].

**Evidence-Based Exercise**

In 26 study groups with HTN patients, the effect of endurance training on blood pressure was -8.3/-5.2[66]. Other studies have found reductions in blood pressure due to chronic and acute exercise to be -7.4/-5.8 mmHg[67] and -3.2/-1.8 mmHg[68], respectively. Mechanisms of vascular, neuro-hormonal, and structural changes contribute to the decreases in blood pressure that result from acute and chronic endurance exercise[66]. Since catecholamines, in particular norepinephrine release, mediate vasoconstriction and increase vascular resistance, reductions in norepinephrine attenuate vasoconstriction and lead to reduction in blood pressure. Declines in plasma norepinephrine have been reported after training by 28.7%[69]. Furthermore, training also decreases endothelin-1, a potent vasoconstrictor, associated with endothelial dysfunction in HTN.

Evidence suggests that nitric oxide plays a major role in moderating blood pressure and impaired nitric oxide activity is an important component in HTN[70]. Regular exercise training improves endothelial responses and vasodilatory function through enhances in nitric oxide availability in both animal and human studies[71]. Indeed, the beneficial effects induced by aerobic exercise training in vascular changes observed in HTN are mainly mediated by a reduction of oxidative stress and increased antioxidant defenses[72,73].

Hyperinsulinemia and insulin resistance are associated with HTN and activation of the sympathetic nervous system. Exercise training improves insulin sensitivity[6,69,74] and this may be important mechanism in mediating reductions in sympathetic outflow and blood pressure. Furthermore, elevated sympathetic nerve activity, as seen with HTN patients, has been associated with increases in arterial wall thickening and vascular stiffness[72,75]. Yet, a recent longitudinal training study confirmed intima-media thickness and the intima-media thickness/lumen ratio were reduced with exercise[75]. Training-induced decreases in sympathetic nerve activity may be beneficial in preventing vascular remodeling that is associated with HTN.

Left ventricular hypertrophy can be present in patients with HTN, especially those who are obese, which can lead to a number of adverse conditions, such as ventricular dysrhythmias, diastolic ventricular dysfunction, cardiac mortality, and risk of sudden cardiac death[76–78]. Findings reveal that endurance exercise training of mild-to-moderate intensity can induce a partial regression of left ventricular hypertrophy with reduction in left ventricle mass index and relative wall thickness in older adults with mild HTN[79]. Data from this study also suggests that the extent of this reversal is likely to be similar to that induced by thiazide diuretics.

**Adverse Effects to Exercise**

According to Hypertension Canada Guidelines[80], due to an acute increase in blood pressure and potential use of the Valsalva manoeuvre during weight training, there are concerns this form of exercise could adversely raise blood pressure levels, leading to an increased risk of hemorrhagic stroke or subarachnoid hemorrhage. Aortic stiffening is strongly associated with age and is the driving force of isolated systolic hypertension[81]. Endothelial dysfunction and increased stiffness of large arteries contribute to development of a HTN response to exercise[82]. Nevertheless, strength training is recommended among exercise specialists for hypertensive individuals (Table 1) with close attention towards proper breathing.

**Table 1 FITT Formula for Hypertensive Patients**[74,83,84]

| | Aerobic | Resistance | Flexibility |
|---|---|---|---|
| **F** | 3-5 d/wk | 2-3 d/wk | 2-7 d/wk |
| **I** | 40-<60% HRR | 30-90% 1RM, 8-12 reps | Hold 30 sec |
| **T** | ≥30 min/d or 3-6 bouts of >10 mins or 150 min/wk | 3-4 sets or 20-60 min/d | Pre/post exercise |
| **T** | Brisk walking, jogging, cycling, swimming | Machine weights, free weights, circuit training | Dynamic, static, yoga, Pilates |

HRR = heart rate reserve
1RM = one-repetition maximum

Diuretics in high doses can interfere with fluid and electrolyte balance[85], and similar symptoms can be exacerbated with high-intensity exercise. If not properly hydrated with attention towards individuals' perceived exertion while engaging in high intensity or long duration activities, HTN patients could experience severe fatigue, dehydration, nausea, and dizziness. Take caution when exercising in extreme environments, such as on a hot day or hot yoga, as HTN can make it difficult for your body to regulate its temperature.

## TYPE 2 DIABETES MELLITUS

### Background

Diabetes is a metabolic disorder affecting approximately 29.1 million people (9.3%) of the U.S. population[86]. There are two types of the disease, namely type I diabetes mellitus and type II diabetes mellitus (T2DM), the latter accounting for nearly 90% of diabetic cases. T2DM results from defects in insulin secretion associated with insulin resistance, leading to increased glucagon secretion and a subsequent rise in blood glucose[87]. Increases in fasting insulin, fasting glucose, SBP, DBP, triglycerides, and body fat percentage are associated with increased risk of developing diabetes[88,89]. Prolonged elevated blood sugar can cause several serious and even life-threatening diabetes-related complications, including kidney disease, foot issues, non-traumatic lower limb amputation, retinopathy, myocardial ischemia, and stroke[86].

### Evidence-Based Medications

Currently available therapies offer a large panel of complementary drugs and some of the more widely used are biguanides, sulfonylureas (SU), and insulin therapy. Trends in prescription drug use among U.S. adults from 1999-2012 showed the use of biguanides increased from 2% to 5.5%, SUs from 2.6% to 3.2%, and insulin therapy from 1.1% to 2.6%[14].

#### *Biguanides*

Biguanides lower blood glucose levels primarily by decreasing the amount of glucose produced by the liver. Metformin, a recommended first-line oral therapy for T2DM[90], is a biguanide that helps to reduce blood glucose by specifically reducing hepatic gluconeogenesis and opposing glucagon-mediated signaling in the liver[91]. When compared to placebo, metformin has

been recorded to reduce glycated hemoglobin (HbA1c) levels by approximately 1% after 3 months of therapy[92]. While the complete mechanisms of metformin appear complex and remain a topic of debate, considerable efforts are continuing to be made to better understand the cellular and molecular modes of action[90]. Various works suggest inhibition of the mitochondrial respiratory chain (Complex I), activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) and reduced activation of protein kinase A (PKA) as potential mechanisms[90,93].

The polarity of metformin makes it dependent on membrane transporters for cellular uptake and secretion[91]. The mechanisms of enhanced glucose uptake via increased translocation of glucose transporters have been linked to activity of GLUT4 and GLUT1, in particular[91,94]. GLUT1 is a glucose transporter across plasma membranes, while GLUT4 is a glucose transporter in skeletal muscle, making it more sensitive to insulin so glucose can be absorbed[91].

*Sulfonylureas*

SUs are among the most frequently used second-line anti-diabetic agents[95], and along with metformin are the most commonly used pharmacological treatments for T2DM[96,97]. SUs stimulate the β cells of the pancreas to release more insulin by binding to and inhibiting potassium flux through ATP-dependent potassium channels[96]. Calcium channels are then opened leading to an influx of calcium and enhanced secretion of insulin from the pancreas[98,99]. Furthermore, it has been shown that SUs interact with the nucleotide exchange factor, Epac2, which interacts with Rap1 protein to increase availability of insulin vesicles[100,101]. Data from six separate studies show SUs to have an average reduction of HbA1c levels of 1.25% after 2 years of therapy[92].

*Insulin therapy*

Insulin administration, typically given by subcutaneous injection can be used to achieve optimum glycemic goals. Secreted from pancreatic β cells, insulin promotes the uptake of glucose by the liver and an improved lipid profile, as well as reduces HbA1c levels by up to 4.9% when used in combination with metformin[102].

**Adverse Effects to Medications**

*Biguanides*

There has been concern over the adverse side effects of metformin; however, some reports indicate that they are negligible when its benefits are brought into account[93]. Gastrointestinal intolerance, the most frequent adverse effect, including symptoms of nausea, diarrhea, and abdominal cramping occurring in up to 50% of treated patients, usually improve or subside as treatment is continued[93,103].

A main problem for metformin users is lactic acidosis, a buildup of lactate in the plasma, which can be accompanied by dizziness, severe drowsiness, muscle pain, tiredness, chills, blue/cold skin, difficult breathing, irregular heartbeat, and stomach pain[103]. While more likely to occur in patients with certain medical conditions, such as renal dysfunction, researchers say it is difficult to determine to what extent, if any, metformin may contribute to the development of lactic acidosis in any case. Still, renal and kidney diseases in T2DM patients have been found to affect approximately 40% of individuals[104]. Several researchers, on the other hand, found no greater risk of lactic acidosis among metformin users with incidence rates ranging between 3-10 per 100,000 person-years[105,106]. However, to date, cases of lactic acidosis continue to be reported in patients taking metformin[107].

Majority of evidence regarding the risk of kidney problems associated with metformin use has been inconclusive[108]. However, in a nationwide cohort study in Denmark, Carlson et al.[109] found the risk of acute dialysis associated with initiation of metformin in patients with T2DM was associated with a 50% increase in risk compared to SUs, corresponding to an absolute risk difference of 50 per 100,000, and a number needed to harm of 1988. This increased risk was greater with women, older patients, patients initiating anti-diabetic treatment at higher doses and in patients with pre-existing renal insufficiency.

*Sulfonylureas*

First-generation SUs have declining uses owing to a high incidence of adverse side effects, such as hypoglycemia in patients with acute or chronic kidney disease, hyponatremia, water retention, and weight gain[93,96,98]. Symptoms of hypoglycemia include polydipsia, polyuria, rapid breathing, flushing, confusion, and drowsiness[103]. Bodmer et al.[106] found the odds ratio of developing hypoglycemia in association with SUs use was 3.73 compared with controls, leading to higher odds than metformin and other oral anti-diabetes drugs.

A systematic review of 77 studies found that SUs can significantly increase the risk of cancer in T2DM compared with metformin[95]. While 33 RCTs did not report a difference in the risk of malignant tumor between SU-treated T2DM and controls, 27 cohort studies showed the cancer risk was higher in patients using SUs than metformin and 17 case-control studies suggested a trend for increased risk in those using SUs compared with non-SU users. Contrary to this finding, an earlier study found no evidence that SUs were associated with cancer risk[110].

*Insulin therapy*

Patient regimes can vary from single daily injections to multiple injections, which can be painful and necessitates self-monitoring of glucose levels. Furthermore, this type of therapy is associated with weight gain and hypoglycemia, the latter of which increases in risk with duration of treatment[111,112]. Insulin therapy was related to an average weight gain of 4 kilograms[113] and can lead to withdrawal from treatment.

**Evidence-Based Exercise**

T2DM can be effectively prevented or delayed by lifestyle changes targeting diet and physical activity improvements, including both resistance and aerobic exercises[114,115]. Meigs[116] claims the best prediction model for T2DM included high sensitivity C-reactive protein (hs-CRP), adiponectin, interleukin-2 receptor A, ferritin, glucose, and insulin, while other studies support additional biomarkers of blood pressure, serum lipids (triglycerides, HDL and LDL cholesterol, total cholesterol), and HbA1c[117]. A meta-analysis of 13 studies investigating the influence of exercise on obese T2DM patients revealed that concentrations of hs-CRP, triglycerides, DBP, SBP, and HbA1c were reduced with exercise intervention[118]. In addition, there was a significant increase of HDL cholesterol in subjects, although this effect has failed to show in other studies[88].

Diabetes Canada Guidelines[119] define "prediabetes" as referring to an HbA1c of 6.0% to 6.4%, placing individuals at high risk of developing diabetes and its complications. In fact, The Epic-Norfolk Trial[120], a prospective study of 4662 men aged 45-79 years, reported an increased risk of death equivalent to 28% for every 1% increase in HbA1c above 5%, independent of other factors such as smoking, age, blood pressure, and lipid profile reports[85,89,121,122]. A Cochrane Review[121] examined 14 RCTs that compared exercise against no exercise in T2DM found exercise

intervention significantly improved glycemic control as indicated by a decrease in HbA1c levels of 0.6%.

Elevated concentration of hs-CRP reflects systemic inflammation, is correlated with abdominal obesity[123], and is closely related to increased risk of diabetes and CVD[124–126]. Serum hs-CRP has been demonstrated as being positively correlated with HbA1c in T2DM patients, and furthermore, is recommended as a predictive laboratory marker for CVD risk in DM patients[126,127]. In 824 patients included in a meta-analysis, Hayashino[124] found exercise was associated with a significant decrease in hs-CRP (-0.66 mg/l), and similar changes have been noted in other studies[128,129].

Inflammation is an important feature of metabolic diseases and diabetes. It has been shown that innate immunity, stress, and inflammation are primary factors in the development of obesity-related insulin resistance in T2DM[130]. In fact, compared to type 1 diabetes patients, those with T2DM generally test positive for serum pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α. Effects of regular physical activity have led to decreases in tumor necrosis factor-α, hs-CRP, interferon gamma, interleukin-1, and interleukin-6. Indeed, Pischon et al.[131] showed that for interleukin-6, exercise was more effective in marker reduction in those with longer duration in exercise programs and a larger number of exercise sessions during the study. Even though these and additional markers of pro-inflammatory cytokines have been shown to increase after strenuous exercise[132], these results support an overall anti-inflammatory role and glycemic control of regular physical activity.

Despite clear metabolic effects of training, several studies show no significant effect on body weight or BMI in T2DM subjects[121,133,134]. Experts suggest this is likely owing to differences in fat mass and lean mass not being interpreted[133,135]. Others found waist circumference and body

fat measurements as better predictors of insulin resistance in T2DM[136,137]. Lee[138] measured total and regional adiposity and skeletal muscle mass and composition in lean men and obese men with and without T2DM using MRI and CT modalities. While body weight did not change in response to exercise, significant reductions in total, abdominal subcutaneous, and visceral fat were observed in all groups. Reductions in visceral fat were greater in the obese and T2DM groups compared to the lean group.

Lewis et al.[139] measured over 200 metabolites in human plasma before and after exercise. While fitness level is one of the strongest predictors of all-cause mortality in people with diabetes[140], researchers found exercise-induced increases in glycerol strongly related to fitness levels in normal individuals[139]. Interestingly, researchers also found several metabolites that increased in plasma in response to exercise, namely glycerol (lipolysis), niacinamide (modulator of insulin sensitivity), glucose-6-phosphate (indicator of glycogenolysis), pantothenate (fatty acid oxidation), and succinate (TAC span 2 expansion), all which up-regulated the expression of nur77, a transcriptional regulator of glucose utilization and lipid metabolism genes in skeletal muscle in vitro. Nur77 has been suggested as a potential therapeutic target for the metabolic syndrome, as its expression in skeletal muscle is reduced in several models of T2DM and is increased in response to insulin-sensitizing treatments[141].

**Adverse Effects to Exercise**

Concerns about the safety resistance training in middle-aged and older people who are at risk of CVDs such as diabetics continue, especially at higher intensities. Acute rises in blood pressure associated with higher-intensity resistance exercise may be harmful, possibly resulting in stroke, myocardial ischemia, or retinal hemorrhage[142]. However, there is a lack of evidence that

resistance training increases these risks and no serious adverse events have been reported with T2DM patients[142,143].

Pederson and Saltin[144] note that most patients with T2DM can engage in physical activity without following particular instructions; however, it is of import that patients treated with SUs, for example, receive guidance in order to avoid hypoglycemia. A systematic review of 12 trials investigating exercise with T2DM patients found hypoglycemia to be among the most commonly reported adverse events as well as back pain, shoulder pain, musculoskeletal injury, tendonitis, and other musculoskeletal discomforts[114]. A similar review found no adverse effects of exercise reported among 377 T2DM individuals[133].

**Table 2 FITT Formula for Type 2 Diabetes Mellitus Patients**[142,145]

| | Aerobic | Resistance | Flexibility |
|---|---|---|---|
| **F** | 3-5 d/wk | 3 d/wk | 2-7 d/wk |
| **I** | 50-70% $HR_{max}$ or >70% $HR_{max}$ | 50-70% 1RM, 8-12 reps | Hold 10-30 sec |
| **T** | ≥30 min/d or 150 min/wk$^{\Psi}$ or 90 min/wk$^{t}$ | 3 sets | Pre/post exercise |
| **T** | Brisk walking, jogging, cycling, dancing, swimming, stair climbing | Machine weights, free weights, resistance bands, body weight, calisthenics | Static or dynamic, yoga, Pilates, Tai chi, balance |

$HR_{max}$ = heart rate maximum

1RM = one-repetition maximum

$^{\Psi}$ moderate intensity

$^{t}$ vigorous intensity

T2DM patients may develop autonomic neuropathy, which can affect heart rate response to exercise and scores in ratings of perceived exertion[146]. While walking or running may be a convenient type of exercise, some T2DM patients, especially those with foot issues should consider low-impact, non-weight bearing activities, such as swimming or cycling (Table 2). After

a 3-month follow-up of a walking program invention, maximum walking distances in diabetics were found to be drastically less than non-diabetic patients[147]. Additionally, the non-diabetic group demonstrated a significant increase in pain-free walking at follow-up compared to the diabetic group.

## OSTEOPOROSIS

### Background

Osteoporosis is a skeletal disorder due to compromised bone strength, leading to increased bone weakness and risk of fractures[148]. According to the World Health Organization[149], osteoporosis is defined as having a bone mineral density (BMD) ≥2.5 standard deviations below the mean for young white adult women, usually measured by dual energy X-ray absorptiometry or diagnostic criteria based on the T-score for BMD (T-score <-2.5 SD).

British Columbia Guidelines[150] emphasize multivariate risk fracture using a risk assessment tool FRAX or CAROC, as BMD only explains a portion of fracture risk. Additional components such as biochemical markers and clinical risk factors that influence fragility and fracture risk are used and often include female sex, increased age, estrogen deficiency, steroid use, low weight and BMI, family history of osteoporosis, smoking, and history of prior fracture[148,151]. Fractures due to osteoporosis can occur at any skeletal site, but most often at the hip, spine, wrist and vertebrae, and are a significant cause of mortality and morbidity in the Western hemisphere[152,153]. The lifelong risk of having a fracture related to osteoporosis is approximately 1 in 2 for women and 1 in 4 for men[154]. It is more prevalent in women especially after menopause when estrogen level decreases, as sex steroids secreted during puberty substantially increase BMD and peak bone mass.

### Evidence-Based Medications

Fracture prevention is the primary treatment goal for patients with osteoporosis[148]. Bisphosphonates (BPs) have been the most widely prescribed and best-studied osteoporosis medication[155,156]. Denosumab (Prolia®) was more recently added to the list of first-line agents,

while selective estrogen receptor modulators (SERMs), and synthetic parathyroid hormone (PTH) remain as common second-line agents[157].

*BPs*

This class of drug has proven efficacy in the prevention of bone loss and in the reduction of fractures in postmenopausal women and men with established osteoporosis[158]. There are four types currently approved for use: alendronate (Fosamax), etidronate (Didrocal), risedronate (Actonel), and zoledronic (Aclasta)[159,160]. These drugs offer clinical benefit to several conditions where there lies an imbalance between bone formation via osteoblasts and bone resorption via osteoclasts, including osteoporosis[156]. BPs show a spine BMD gain of 4-9% and fracture reduction of 30-70%[161]. Alendronate, risedronate, and zoledronic acid are more commonly used because they reduce risk of fractures in all bones. In comparison, etidronate is the oldest and least preferred because it is not as effective and only reduces fracture risk in the spine[160].

When received orally or through intravenous injection, BPs inhibit hydroxyapatite breakdown, leading to an antiresorptive effect through the reduction of soft tissue calcification and normal calcification[156,162]. Due to their high affinity to bone mineral, BPs have a high degree of target organ specificity over other body tissues, leading to preferential uptake into bone[158]. Once absorbed, the drug is taken-up by osteoclasts, inhibiting key enzymes in the mevalonic acid pathway and leading to disruption of signaling molecules (GTPases) in osteoclastic function, finally ending in osteoclast cell apoptosis.

*Denosumab*

Denosumab, a fully human monoclonal antibody is a relatively newer medication shown to reduce osteoporotic fracture in men and women[160]. In the FREEDOM trial[163], 7868

postmenopausal women with osteoporosis were assigned placebo or denosumab for 36 months. Cumulative incidence of fractures in the treatment group was 2.3%, while in the placebo group was 7.2%. Although BPs are typically preferred as initial therapy for osteoporosis, denosumab can be used as initial therapy in select patients at high risk of fracture, including older patients who have difficulty with dosing requirements of oral BPs, those who are intolerant or unresponsive to other therapies, and those with impaired renal function[164]. Denosumab binds avidly to RANK ligand (nuclear factor-κB ligand), a soluble protein, preventing interaction of RANK ligand with its receptor, RANK, which is present on the surface of osteoclasts and their precursors[165]. By inhibiting osteoclast activity, the drug decreases bone resorption in trabecular and cortical bone and increases bone mass and strength[165,166].

*SERMs*

During menopause, women's estrogen level decreases, leading to a reduction in bone density. While SERMs are non-hormonal, they are able to produce estrogenic and antiestrogenic effects depending on the area of the body[167]. In bone, they regulate bone metabolism through estrogen receptors on osteoblasts by binding to estrogen receptor α or β subunits and decrease osteoclast activity while also maintaining physiological function of osteoblasts[168,169].

Raloxifene (Evista®), an oral SERM, showed to increase bone density and prevent fractures of the spine in postmenopausal women by 30-50%[170,171]. However, reductions in fracture risk have not been observed in other fracture areas with this drug. Bazedoxifene is another type of SERM that has also demonstrated efficacy for prevention and treatment of osteoporosis with lumbar BMD changes ranging from +1.08% to +1.49%[172].

*Synthetic PTH*

Endogenous PTH stimulate bone formation by directly acting on osteoblasts and regulating renal tubular cells in reabsorbing calcium and excreting phosphate[173]. A newer biosynthetic drug, teriparatide, is also an anabolic agent that essentially mimics the physiological effects of PTH[174]. More specifically, binding to G-protein-dependent cell surface receptors induces a cascade that activates several enzymatic pathways involving adenylate cyclase and phospholipases that result in an increase in osteoblasts and decrease in apoptosis[173]. A 2012 meta-analysis[175] showed teriparatide-treated postmenopausal women had a BMD increase of 8.14% in the spine and 2.48% at the hip.

**Adverse effects to Medications**

*BPs*

BPs induce dose-dependent gastrointestinal disturbances, nausea, loose bowels, inflammation and ulceration of the esophagus and stomach, heart burn, and atrial fibrillation; although, the latter does not reveal a consistent association[152,153,158,176]. Acute phase reactions to BPs such as fever, headache, myalgia, arthralgia, and malaise occurring within 24-36 hours and lasting up to 3 days were reported in 18% of subjects receiving intravenous first-doses[158]. Both alendronate and risedronate have shown a small risk to irritation of the esophagus.

BPs have been associated with osteonecrosis of the jaw (ONJ), especially following dental surgeries such as dental extractions[156]. Incidence of patients on BPs suffering from ONJ ranges from 0.5-9.9%[177–180]. It is speculated the likelihood of ONJ is related to the dosage, route, and duration of BP therapy[153]. Results from a case-control study suggested a dose-response relationship was demonstrated over increasing time periods of exposure, where the risk for ONJ significantly increases and odds reaching 5 times higher for those with 1.5-2 years of exposure

compared with those with 0-1.5 years of exposure[178]. Importantly, these researchers noted a significantly reduced risk of ONJ with oral compared to intravenous BP therapy and this has been reported in several other cases[153,156,179,180].

Patients prescribed alendronic acid in particular, have shown an association with atypical femoral fractures[180–183]. This type of fracture occurs mainly in the subtrochanteric region with little or no trauma[180]. Concerns have been raised about potential over-suppression of bone turnover during long-term use of BPs[182]. An investigation of the trends in the incidence of typical and atypical femoral fractures in Australian patients over 50 years of age from 2009 to 2014 found that the atypical-type accounted for half of all femoral shaft fractures[184]. Interestingly, Clout[184] revealed a possible positive trend between the incidence of typical and atypical femoral fractures and the rate of prescription of BPs for osteoporosis over a 13-year period. Still, additional trials are warranted including further understanding of the biological mechanism of atypical femoral fractures in order to identify a clear benefit/risk ratio[185].

*Denosumab*

Safety of denosumab in the treatment of postmenopausal osteoporosis was assessed in a 3-year multinational study[163] including 7808 postmenopausal women. Incidence of all-cause mortality was 2.3% in placebo and 1.8% in Prolia® group. Incidence of nonfatal serious adverse events was 24.2% in placebo and 25% in Prolia®. Back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis were listed as the most common side effects reported; and furthermore, back pain, constipation, and breast cancer were the most common adverse reactions leading to discontinuation of the drug. However, a causal relationship of new malignancies to drug exposure has not been established.

In the abovementioned study by Cummings and Martin[163] serious adverse events of cutaneous infection, like cellulitis and erysipelas were reported more frequently in the Prolia® group. Dermatitis, eczema, and rashes occurred at a significantly higher rate in treated vs. placebo groups (10.8 vs. 8.2%). There was no clear clinical pattern to suggest a relationship to time or duration of exposure to denosumab[186].

Reports of severe symptomatic hypocalcemia after denosumab injection are cited[95]; although, this condition is not typically observed in patients with sufficient calcium and vitamin D levels[164]. While previously reported incidences of hypocalcemia in patients ranged from <0.05% and 12.4% [163], Chen and Smerdely[95] found a rate of 14% development over 6 months, despite majority of patients being treated with calcium and vitamin D supplementation.

*SERMs*

SERMs induce vasomotor symptoms, including hot flashes, leg cramps, and venous thromboembolic events, including deep vein thrombosis and pulmonary embolism[187–190]. In a 3-year study by Silverman et al.[190], postmenopausal osteoporotic women were treated with bazedoxifene 20 mg/d, bazedoxifene 40 mg/d, raloxifene 60 mg/day or placebo. Although fracture incidence was significantly lower with treatment groups compared to placebo, the incidence of adverse effects was higher in the treatment groups. Deep vein thrombosis occurred in 0.4%, 0.5%, 0.4%, and 0.1% of the bazedoxifene 20 mg, bazedoxifene 40 mg, raloxifene 60 mg, and placebo groups, respectively. Corresponding occurrence of leg cramps occurred was 10.9%, 10.9%, 11.7%, and 8.2% in that same order of groups.

A 2-year extension study[188] to Silverman and colleagues' previous study had treatment groups of 20 mg/d, 40/20 mg/d (previous 40 mg/d patients were switched to 20 mg/d after 4 years), and placebo. Raloxifene treatment was discontinued. Results found hot flashes to occur in 13.0%

of the 20mg group and 13.4% of the 40/20 mg group compared to 6.6% of the placebo group of those taking bazedoxifene. Furthermore, 13.6% of the 20mg group, 13.3% of the 40/20mg group, and 10.2% of the placebo group experienced leg cramps. However, most adverse events were mild to moderate in severity and did not result in withdrawal from the study.

*Synthetic PTH*

Most common adverse effects with teriparatide are nausea, headache, vertigo, and leg cramps, which have been shown to cause approximately 6% of users to stop treatment[173,187]. In a study involving teriparatide-treated men with osteoporosis, 9 patients (8.9%) withdrew from the trial due to adverse events, including 7 (4.8%) from the placebo group, 14 (9.3%) in the 20µg dose group and 18 (12.9%) in the 40µg dose group[191]. Nausea was the most common drug-related side effect.

**Evidence-Based Exercise**

Total inactivity results in loss of bone mineral and mass[1,192]. Physical activity promotes changes in the bone metabolism through direct effect via mechanical force. Bone tissue, including highly mechanoreceptive osteocytes, that is subject to a mechanical stimulus responds with a cellular reaction characterized by an acute release of prostaglandins, increasing [cAMP] and leading to production of growth factors and subsequent bone remodeling in response to the original load[192,193]. The indirect effect of exercise on bone is through hormonal influences that consequently increase osteoblast activity[194]. Exercise-induced stimulation of growing hormone has enhanced effects on IGF-1, a citocene that triggers collagen synthesis by the osteogenic cells, increasing bone matrix formation. Older men with low serum IGF-1 have indeed shown to have an increased risk of incident fractures, especially at hip and vertebral sites[195].

While bone mineral and mass that result from endurance or resistance training are relatively small, even small increases can help prevent or delay osteoporosis[196]. A systematic review[197] of the effect of exercise on bone mass in pre- and post-menopausal women showed a positive effect of impact and non-impact exercise on bone mass at both the lumbar spine and the femoral neck. At the lumbar spine, the difference in bone density between exercise and control groups was 1.6% for impact exercises, and 1.0% for non-impact exercises. At the femoral neck, there was a 0.9% improvement for impact exercisers and 1.4% improvement for subjects in non-impact exercise programs. In a separate study, the exercise group showed percent changes in lumbar BMD compared to baseline values of +4.33±1.6% and +4.29±2.34% at 1 and 2 years of exercise training, respectively, which was significantly greater compared to the non-exercising group[198].

Examples of impact and non-impact activities are shown in Table 3, along with aerobic, resistance, and flexibility exercise guidelines for post-menopausal patients with osteoporosis. One of the main goals for exercising with osteoporosis is fall prevention, making it important to focus on controlled progression of exercise frequency and intensity. Activities that may have excessive twisting or flexion of the spine and trunk, such as certain types of yoga are not recommended.

**Table 3 FITT Formula for Post-Menopausal Osteoporosis Patients**[199–201]

| | Aerobic | Resistance | Flexibility |
|---|---|---|---|
| **F** | 3-5 d/wk | 2-3 d/wk | 2-7 d/wk |
| **I** | 50-70% HRR | 50-80% 1RM, 15-20 reps | Hold >30 sec |
| **T** | 30-60 min/day or 150 min/wk | 2 sets | 2 sets or pre/post workout |
| **T** | Low impact (cycling, swimming, kayaking, dancing, tennis) progressing to moderate impact (rope-skipping, two-legged jumps) | Resistance machines, elastic bands, dumbbells, weighted vests, agility | Dynamic or static, Tai chi, Restorative or Yin yoga |

HRR = heart rate reserve
1RM = one-repetition maximum

While endurance and resistance physical activity interventions have shown to have a positive relationship with BMD and an inverse relationship with BMI, BMI itself is strongly predictive of BMD and fracture risk[151,202,203]. The relationship is nonlinear, with the steepest gradient of risk being seen at BMI values <20 kg/m$^2$ and only a small further decrease in risk being seen at levels >25 kg/m$^2$. These risks are largely independent of sex[203]. It is well-established that exercise helps with weight control and is a useful method for maintaining a healthy, optimal BMI through several biological mechanisms such as improved body composition (reduced abdominal adiposity and increased muscle mass) and enhanced lipid profiles (reduced triglycerides and improved cholesterol levels)[204,205].

The main cause of fractures amongst osteoporotic women is falls, due in part to an impaired sense of balance and low levels of muscular strength[206]. Thus, increasing levels of strength and balance achieved by physical exercise plays a key role in fall prevention[207,208]. Otero et al.[209] randomly assigned 65 elderly women with osteoporosis to either an exercise group, consisting of balance and strength training or to a control group which had no exercise component. The exercise group performed balance training and low-intensity strength training for 6 months. Improvements in static balance (21%), dynamic balance (36%) and strength of upper (80%) and lower (47%) limbic in the exercise group in comparison to control group were seen. Fall prevention exercise programs specifically, have been shown to reduce 61% of falls resulting in fractures[210].

**Adverse Effects to Exercise**

There is a subsequent risk of falling while participating in various physical exercises, especially with older men and women, whose balance can worsen with age and those who have limited experience in exercise regimes. Therefore, it is recommended that osteoporotic patients begin training programs under professional supervision. Individuals who are more knowledgeable

about osteoporosis and the factors that influence osteoporosis were found less likely to fall, as well as had higher self-confidence in exercising[211].

Physical activity programs likely need to be modified when specific to osteoporotic patients. Chilibeck et al.[212] systematically reviewed 111 articles and found the incidence for adverse events during physical activity to be 3.4-11% (0.06-2.4% serious adverse events) and included increased joint pain, fracture, and back pain for those with arthritis, osteoporosis, and low back pain respectively. Even with low incidence rates, it is recommended by many professionals that individuals with musculoskeletal conditions avoid heavy load-bearing activities (opt for swimming, or cycling), high-falling risk activities, and powerful trunk flexion/twisting due to increased risk of vertebral compression[135,212].

## DEPRESSION

### Background

Mood disorders are one of the most common mental illnesses, with almost 1 in 9 (11.3%) adults identifying symptoms that meet the criteria for depression at some point in their life[213]. Major depression disorder (MDD) refers to a wide range of mental health problems characterized by the absence of a positive effect, such as a loss of interest and enjoyment in ordinary things and experiences[214]. While conclusive underlying causes of most mood disorders remain unknown, there is a clear heritable factor as evidenced through studies of twins and families[215,216]. Behavioral and physical symptoms include irritability, social withdrawal, thoughts of death or suicide, changes in appetite, fatigue and diminished activity, anxiety, exacerbation of pre-existing pains, and lack of libido[214,217,218]. Apart from the subjective experiences of people with depression, the impact on social and occupational functioning, physical health and mortality is substantial. Depressive illness causes a greater decline in health state than the chronic physical illnesses angina, arthritis, asthma and diabetes[219].

### Evidence-Based Medications

Canadians rank third-highest among 23 developed counties surveyed in consumption of antidepressants[220]. Data shows the U.S. is on a similar path, as the number of Americans on antidepressants more than doubled from 1998 to 2010 (11.2 million to 23.3 million)[221]. Leading up to 2011, the most frequently prescribed antidepressants among U.S. men and women were selective serotonin reuptake inhibitors (SSRIs)[222]. Serotonin norepinephrine reuptake inhibitors (SNRIs) and norepinephrine dopamine reuptake inhibitors (NDRIs) also increased in use during that time period and are commonly used today[14,222] While monoamine oxidase inhibitors (MOIs) and tricyclic antidepressants (TCAs) are alternative drugs for MDD, their increase in prevalence

has been negligible[222], likely a result of their frequently reported negative side-effects[223,224], and thus will not be included.

*SSRIs*

In most cases, the first choice for antidepressant therapy is usually with an SSRI, which includes fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), escitalopram (Cipralex), paroxetine (Paxil) or fluvoxamine (Luvox)[225–227]. SSRIs inhibit reuptake of serotonin into the presynaptic nerve terminals in the brain, resulting in an increase in serotonin concentration and prolonged signaling of the neurotransmitter across synapses[228]. This property is shared with TCAs, but without affecting the other neuroreceptors or fast sodium channels, thus causing fewer side effects[223]. After a sustained drug use of about 3 weeks, the synaptic concentration of serotonin in the cortex reaches therapeutic levels, resulting from a desensitization of the presynaptic inhibitory receptors.

SSRIs are frequently reported in the literature as having a statistically significant effect on depression symptoms[229–233]. A network meta-analysis[234] that compared SSRIs and SNRIs, found sertraline and paroxetine to be statistically significantly superior to placebo in reducing depression scores by at least 50% (odds ratios = 1.28, 1.48, 1.62, respectively). Citalopram (1.07) and fluoxetine (1.08) had the lowest benefit. Other significant benefits have also been published for escitalopram and fluvoxamine[230,235,236].

*SNRIs*

If patients' symptoms suggest norepinephrine imbalance or an intolerance to SSRIs, then SNRIs are often prescribed[226]. This class of medication includes venlafaxine (Effexor), duloxetine (Cymbalta), desvenlafaxine (Pristiq), and milnacipran[224,226]. SNRIs are dual-acting inhibitors,

characterized by a mixed presynaptic inhibition of serotonin and norepinephrine[224]. Venlafaxine also weakly inhibits dopamine reuptake, whereas milnacipran does not. They act on depressive symptoms, as well as on certain comorbid symptoms, like anxiety and sleep disorders.

Meta-analyses suggest that SNRIs have an efficacy advantage compared with SSRIs in MDD[237,238]. Venlafaxine, in particular shows significant advantage over SSRIs in achieving remission and response in MDD treatment[238], while milnacipran has shown no difference [239]. On the other hand, some researchers concluded that SNRIs showed statistical but not clinical significance when compared with SSRIs in treating MDD[240,241]. Although remission rates were higher for SNRIs in almost all 15 trials selected by Machado and Einarson[240], the statistically significant amount of 5-7% between SNRIs and SSRIs was not considered clinically important. It is important to note that even modest difference in antidepressant efficacy, if sustained, may have important public health implications[227].

*NDRIs*

NDRIs, such as Wellbutrin (bupropion) or Zyban are often not first-line treatments in MDD[226]. If patients do not show clear remission of symptoms after 2-3 months of treatment with antidepressants, NDRIs can be used in monotherapy or combination therapy, such as with an SSRI. This drug acts as a reuptake inhibitor for norepinephrine and dopamine by blocking the action of each of their respective transporters, leading to increased extracellular concentrations of both neurotransmitters[242]. Therapeutic doses of bupropion given to depressed patients (N=11) showed reduced whole-body turnover of norepinephrine without altering plasma norepinephrine levels, a finding that indicates significant central noradrenergic activity[243].

Bupropion has been shown to be significantly more efficacious than placebo in the treatment of MDD, reducing Hamilton Depression Rating Scale (HAMD), Clinical Global

Impressions (CGI)-severity and CGI-improvement scores significantly more than placebo in a 4-week and 6-week study[244,245]. In comparison to other antidepressants, bupropion has been shown to be as effective as venlafaxine[246], paroxetine and fluoxetine; although, trends favoring sertraline, escitalopram, and venlafaxine over bupropion have been observed[230].

**Adverse Effects to Medications**

While prescription of antidepressants has been increasing over the last few decades, this trend has been met with some controversy as the ongoing safety and effectiveness of these treatments have sometimes been called into question[226]. According to the Agency for Healthcare Research and Quality[247], majority of people who take antidepressants (63%) experience at least one side effect.

*SSRIs*

Jakobsen et al.[229] found that SSRIs' small potential benefit seemed to be outweighed by their harmful effects. SSRIs had significantly increased risks of serious adverse events (OR 1.37), where 31/1000 SSRI-users will experience a serious adverse event compared with 22/1000 control subjects. SSRIs also increased the number of non-serious adverse events. Due to their pharmacological action, side effects of SSRIs include GI issues, headaches, insomnia, fatigue, anxiety, weight gain, and sexual dysfunction[226,248]. According to Hiernoymus et al.[248], GI complaints, weight loss, and sexual functioning, particularly increased in severity at end point in SSRI-treated patients more frequently than those given placebo (OR 1.27, 1.24, 1.21, respectively).

Nine trials totaling 2,641 MDD patients showed SSRI-treated patients were more likely to experience nausea, hypersomnia, and fatigue than reboxetine-treated patients[249]. In Cipriani et al.'s[230] study, escitalopram and sertraline SSRI classes showed the best profile of acceptability,

leading to significantly fewer discontinuations than did fluvoxamine, paroxetine, and other antidepressants, duloxetine, reboxetine, and venlafaxine. SSRIs and SNRIs were both found to be equally associated with a greater risk of falls and fractures among older adults[250,251].

There has been considerable debate in recent years regarding a potential relationship between SSRI use and suicide rates[252]. Beginning in 2003, the FDA issued advisories and 'Black Box' warnings for SSRIs due to a low but statistically significant increased risk of self-harm and suicidal thoughts in adolescents using the medication[253,254]. However, there have been numerous claims that these warnings may have instead increased young suicides by leaving a number of suicidal adolescents without antidepressant treatment[255,256]. Barbui et al.[257] assessed the risk of suicide in individuals exposed to SSRIs compared to those who were not. Exposure to SSRIs was associated with a decreased suicide risk among adults and older people, but with increased risk among adolescents. However, the data for analysis of adolescent suicide was based on only two studies[258,259]. One year later, Dudley et al.[252] examined observational studies totaling 574 adolescents and did not find an association between SSRI usage and suicide.

*SNRIs*

Common side-effects from SNRIs are nausea, insomnia, dry mouth, sexual dysfunction, weight gain, and increased blood pressure; and in some instances, more so than the SSRI drug class[226,260]. Indeed, Machado and Einarson[240] noted dropout rates due to adverse drug reactions to be 3.2% higher with SNRIs compared to SSRIs. While some researchers say SNRIs' mechanism of action allow them to be better tolerated with limited adverse effects compared to other antidepressants like TCAs or MOIs[224], other researchers found its pharmacodynamic characteristics the reason for an elevated number of venlafaxine-users experiencing nausea, dry mouth, dizziness, hyperhidrosis, insomnia, constipation, tremor, and sexual dysfunction[260].

Dizziness, in particular, has been found to have a greater association with venlafaxine and duloxetine compared to sertraline and placebo[234].

*NDRIs*

Since bupropion is a NDRI with no serotonergic activity, common antidepressant-associated side effects such as sexual dysfunction, weight gain and sedation are not associated with this drug class[242]. However, one study found increased rates of dry mouth, insomnia, and hyperhidrosis in bupropion XR-treated groups, consistent with its catecholaminergic mechanism[260].

There is a dose-dependent risk of seizures associated with bupropion, which initially removed it from the market before being re-instating after it was found that lower doses were safer[226]. A recent case report of a 53-year-old woman medicated with bupropion, sertraline and risperidone experienced spontaneous seizures after electroconvulsive therapy[261]. Researchers concluded that bupropion's pharmacological characteristics and the clinical evolution of the case suggest that the drug had a major influence on the spontaneous seizures, although the patient was also medicated with two other drugs. An earlier study found that bupropion IR dosages of 300-450 mg/day are associated with a seizure rate of 0.4% and seizure rates occur at a greater rate above this dosage[262]. Meanwhile, other formulations of bupropion (bupropion SR and bupropion XR) have shown lessened seizure rates similar to other antidepressants.

**Evidence-Based Exercise**

While depression is commonly treated with antidepressants, not all individuals respond to treatment and only 50-70% of treated patients have complete remission of symptoms[263]. Therefore, some people may prefer alternative approaches, such as physical activity. Exercise has been shown

to be efficacious as a separate[264,265] and as a supplemental[266–269] treatment for MDD. One-hundred and fifty individuals with treatment-resistant MDD were randomly assigned to a usual pharmacology group or a usual pharmacology group plus aerobic exercise group[268]. After 12 weeks, the exercise group showed improvement of all depression and functioning assessments, as indicated by lower 17-item HAMD, Beck Depression Inventory, and CGI-severity scale and higher Global Assessment of Functioning scores compared to both baseline values and to control group.

Moreover, efficacy of patients engaging in exercise seems generally comparable with patients receiving antidepressant medication. Blumenthal and colleagues[266] found that after 4 months of treatment, patients receiving active treatments had higher remission rates than placebo controls and comparable rates to the medication group (supervised exercise = 45%, home-based exercise = 40%, medication = 47%, placebo = 31%). All treatment groups had lower HAMD scores after treatment. An earlier study by Blumenthal[270] discovered that although medication facilitated a more rapid initial therapeutic response than exercise, after 16 weeks of treatment exercise was equally effective in reducing depression among patients with MDD. These beneficial effects have even been shown with just 30 minutes of treadmill walking for 10 consecutive days[271].

An important correlate of functioning is quality of life, which is described as individuals self-assessments of their feelings regarding their function and ability to derive pleasure from life's activities[272]. Depression has a marked impact on an individual's mental and physical health leading to considerable impairment in several domains of quality of life[273]. A recent meta-analysis[273] found that exercise improves physical (i.e. dependence on medicinal substances, energy and fatigue, pain and discomfort) and psychological (i.e. self-esteem, negative feelings, positive feelings) domains and overall quality of life in people with depression. No effect was observed across social (i.e. relationships, social support, sexual activity) or environmental (i.e. financial resources, physical

safety, freedom) domains. Pharmacological treatments have shown benefits, though they are often not sufficient to return the quality of life of depressed patients to premorbid levels and some patients still experience impairment in quality of life, even after remission of symptoms[274].

Early research in the efficacy of exercise in reducing depression symptoms suffered from a variety of methodological issues, such as small samples and inadequate blinding, and thus have been heavily criticized[275–277]. More recently, researchers have been conducting meta-analyses with effect sizes ranging from moderate to large[264,278]. Using extensive search procedures, Rethorst et al.[264] found an overall effect size in 58 randomized trials to be -0.80 (95% CI -0.92, 0.67), indicating that subjects in the exercise treatment had significantly lower depression scores than those receiving control treatment. North et al.[279] and others[280] noted that larger effects are associated with longer intervention duration and more exercise sessions.

The full mechanism by which physical activity may reduce depressive symptoms is not well understood[276,281,282]. Many physiological explanations include thermogenesis, anti-inflammatory cytokines, neurotrophic factor, endorphins, and brain neurotransmitters[264,276,281,283]. Temperature increases in specific brain regions due to physical exertion can lead to feelings of relaxation and reduction in muscular tension[284]. Exercise has been shown to be broadly anti-inflammatory and it has been suggested that pro-inflammatory cytokines have potential for biomarker development in MDD[285,286]. However, Rethorst et al.[285] did not find exercise significantly changed mean cytokine level in MDD patients. Studies investigating exercise-induced effects on brain derived neurotrophic factor have shown mixed results[263,287], yet exercise-induced decreases in thiobarbituric acid-reactive substances, a marker of oxidative stress that plays a role in depression has been observed[287]. Endorphins, which are related to positive mood and an

overall sense of well-being have been shown to increase in plasma levels, but researchers question whether this is reflective of brain chemistry[276].

The more popular belief, the monoamine hypothesis, accredits increases in brain neurotransmitters (serotonin, dopamine, and norepinephrine) with exercise, levels of which are usually diminished in depressive patients[288]. Findings from older animal studies[289,290] showing associations between monoamines and exercise has prompted curiosity as to whether these same effects are seen in humans; yet, this effect failed to show in a recent RTC by Carneiro and colleagues[291]. Nonetheless, The United Kingdom's National Institute for Health and Clinical Excellence[214] published a depression treatment guide that recommends exercise rather than antidepressants.

**Adverse Effects to Exercise**

There are limited reports of MDD patients experiencing adverse effects to exercise. Several studies investigating exercise treatment with depressed patients report an absence of negative side effects of exercise, such as muscle pain, tightness, or fatigue[264,292–294]. Rethorst et al.[264] found that out of 58 studies, only 16 reported participants' dropout rates and they were not statistically different between the exercise plus antidepressant group and the antidepressant only group (14.6% vs. 11.4%).

Interestingly, a research team at Columbia University discovered that there is an optimal amount of physical activity associated with better mental health[298]. Those who exercised less than 2.5 hours per week or more than 7.5 hours per week had more symptoms of depression, anxiety, or poor mental health. People who engaged in the recommended amount of exercise of 2.5-7.5 hours per week were about 139 times more likely to have better mental health. Other studies have

reported similar recommendations regarding the frequency and length of physical exercise (Table 4), including activities that involve mindfulness mental training, such as Tai chi.

**Table 4 FITT Formula for Depressive Patients**[295–297]

| | Aerobic | Resistance | Flexibility |
|---|---|---|---|
| **F** | 3-5 d/wk | 2-3 d/wk | 2-7 d/wk |
| **I** | 50-90% $HR_{max}$ or 50-70% HRR | 10-15 reps | Hold 10-30 sec |
| **T** | 30-60 min/day or 3-6 bouts of >10 min or 150 min/wk | 2-3 sets | 3-4 sets |
| **T** | Brisk walking, running, cycling, swimming, sports | Machine weights, free weights, resistance bands, body weight | Static or dynamic, Tai chi, yoga |

$HR_{max}$ = maximum heart rate
HRR = heart rate reserve

## BREAST CANCER

### Background

Breast cancer is a complex disease most commonly affecting the inner lining of milk ducts (ductal carcinoma) or the lobules that supply the ducts with milk (lobular carcinoma)[299]. According to the Canadian Cancer Statistics Advisory Committee[300], breast cancer will affect 1 in 8 Canadian women during their lifetime, making it the second leading cause of death from cancer in Canadian women. Although not as common, breast cancer can develop in men. Many factors known to increase the risk of breast cancer are modifiable, such as alcohol use, whereas others are not modifiable, such as age. There are numerous personal (i.e. hormone levels), family (i.e. BCRA1 or BCRA2 gene), reproductive (i.e. breastfeeding), lifestyle (i.e. diet) and environmental (i.e. chemical exposure) factors that studies show may increase breast cancer risk[301]. Typical symptoms for breast cancer include a lump found in the breast or armpit, and examples of alerting features include swelling of the breast, nipple discharge or pain, and persistent tenderness or unusual discomfort.

### Evidence-Based Medications

There are several ways to treat breast cancer, often depending on the patient's overall health, medical history, age, type and stage of the cancer, and tolerance for certain medications[301]. Local treatments include surgery and radiation therapy, while systemic treatments include chemotherapy, hormone therapy, and targeted therapy. When diagnosed, patients may receive more than one type of therapy.

*Surgery*

Surgical treatment for breast cancer usually involves breast conserving surgery (lumpectomy or partial mastectomy) or mastectomy, depending on the stage and type of the tumor[301]. The presence of any cancer cells in the lymph nodes will help determine the need for subsequent surgery, radiation, and medical treatments. Sixty-one percent of women diagnosed with early stage (I or II) breast cancer have breast conserving surgery, 45% have mastectomy, 1% have radiation or chemotherapy without surgery, and 2% do not receive any treatment[302]. Among women with stage III or IV breast cancer, 14% undergo breast-conserving surgery, 45% have mastectomy, 26% receive radiation and/or chemotherapy without surgery, and 16% do not receive any of these treatments. It was found that 8-year overall survival values for N0 and N1 patients were highest for breast-conserving surgery plus radiotherapy than mastectomy alone or mastectomy plus radiotherapy[303].

*Radiation*

Radiation therapy is the use of high-energy particles or waves to kill cancer cells by damaging their DNA[304]. However, radiation therapy can also damage normal cells, leading to dismal side-effects. Breast conserving surgery is almost always followed by radiation therapy because it has been shown to reduce the risk of breast cancer recurrence significantly[303,305,306]. Radiotherapy reduced the 10-year risk of any first reoccurrence from 35% to 19.3% and reduced 15-year risk of breast cancer death from 25.2% to 21.4%[305]. Radiation can also be used in combination with chemotherapy[307].

*Chemotherapy*

Chemotherapy involves the use of a combination of anti-cancer drugs to treat cancerous cells, usually orally or through intravenous[301]. The benefit of chemotherapy is dependent on multiple factors, including the size of the tumor, the number of lymph nodes involved, the presence of estrogen or progesterone receptors, and the amount of human epidermal growth factor receptor 2 (HER2) protein made by the cancer cells. Anthracycline-based chemotherapy, including doxorubicin and epirubicin have been the cornerstone of breast cancer chemotherapy in both adjuvant and metastatic settings showing positive results after patient follow-ups ranging between 5 to 10 years[308]. Multiple mechanisms have been proposed to explain the cytostatic and cytotoxic action, which include free radical formation, lipid peroxidation, direct membrane effects, and most notably, interactions with DNA-topoisomerase II complex which disturbs DNA replication and transcription[309]. The addition of taxanes to anthracycline-based chemotherapy as adjuvant therapy reduces risk of recurrence and overall mortality by 4.6% and 3.2%, respectively[310].

*Hormone Therapy*

Breast cancer is a hormone-dependent tumor and estrogen is known to play a major role in the initiation and progression of the disease[311]. About two-thirds of breast cancer diagnoses are hormone receptor-positive (estrogen or progesterone) and high estrogen levels help these cancer cells grow and spread[312]. Adjuvant endocrine therapy in early breast cancer significantly reduces the risk of breast cancer recurrence and improves overall survival[313]. Tamoxifen is the recommended treatment in premenopausal women, whereas aromatase inhibitors have demonstrated superiority compared with tamoxifen in postmenopausal women[314–316]. While tamoxifen inhibits activity of estrogen by binding to estrogen receptors, aromatase inhibitors block conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma[302,316].

Treatment of estrogen receptor-positive breast cancer with tamoxifen for at least 5 years has been shown to reduce the rate of recurrence by approximately 40-50% throughout the first decade, and reduces breast cancer mortality by about one-third throughout the first 15 years[317]. Clinical trials in postmenopausal women have demonstrated a small advantage to including an aromatase inhibitor initially or over the course of treatment rather than 5 years of tamoxifen alone[318].

*Targeted Therapy*

Cancer cells with increased amounts of HER2 protein on their surface tend to grow and spread more aggressively[319]. HER2 is overexpressed in 25% to 30% of invasive breast cancers[320] and elevated HER2 levels correlate strongly with the pathogenesis and prognosis of breast cancer[302,319]. Several drugs can be used to target HER2, such as trastuzumab (Herceptin), pertuzumab (Perjeta), lapatinib (Tykerb), and ado-trastuzumab emtansine (Kadclya)[301].

Trastuzumab is the standard of care in patients with HER2-postive breast cancer in any treatment setting[321]. The first humanized monoclonal antibody targeted to bind to HER2, trastuzumab reduces signaling in phosphatidylinositol 3-kinase and mitogen-activated protein kinase pathways, leading to cell apoptosis[322]. The combined results of two large trials indicate that adding trastuzumab to standard chemotherapy for early stage HER2-positive breast cancer reduces the risk of recurrence and death by 52% and 33%, respectively compared to chemotherapy alone[323]. Pertuzumab, which binds to a different location on HER2 protein than trastuzumab, has also shown promising effects[324]. Lapatinib has been approved in combination with capecitabine chemotherapy in treatment of patients with trastuzumab-resistant breast cancer[319,325]. The EMILIA trial[326] cited proven value in ado-trastuzumab emtansine with patients previously treated with trastuzumab and taxane showing significant improvement in objective response rate, progression-free survival, and overall survival.

**Adverse Effects to Medications**

Studies have shown that between 25-60% of women develop chronic pain after breast cancer treatment[327–329] and may also experience cognitive impairments and chronic fatigue[330,331].

*Surgery*

Following surgery and/or radiation, potential side-effects include numbness, tingling, or tightness in the chest wall, arms or shoulders[302]. Surgery and radiation therapy involving the axillary lymph nodes can lead to lymphedema, a serious swelling of the arm caused by retention of lymph fluid that can impair arm function[332,333]. Lymphedema ranks high among breast cancer survivors' concerns affecting about 20% of women who undergo axillary lymph node dissection and 6% of patients who receive sentinel lymph node biopsy[334]. Symptoms associated with lymphedema include heaviness, tightness, pain, cramps, and a crawling sensation[335]. Lymphedema can lead to progressive swelling, fibrosis of soft tissues, neurologic changes and infection[336]. Ninety-two percent of breast (n=55) and cervical (n=8) cancer patients with stage II secondary lymphedema rated their pain as moderate to severe[335].

*Radiation*

While radiation destroys cancer cells, it can also harm healthy cells and can negatively impact patients' quality of life significantly more than control[337,338]. Radiotherapy-induced skin [339] and cardiac toxicity[340] remain a serious clinical problem that affects many patients with breast cancer undergoing adjuvant radiotherapy. Acute and chronic toxicities have been noted in patients treated with adjuvant breast or chest wall radiation therapy, including skin (30-40%), lung (3/%) and heart toxicity (1.5%)[341–343]. Two separate studies included women treated with radiotherapy for breast cancer and both showed a significantly increased risk of cardiac mortality after left-side

irradiation[341,344]. Furthermore, while radiotherapy for early breast cancer can decrease breast cancer mortality, it can also increase other mortality, mainly from heart disease and lung cancer[339,345].

Fatigue was found to be the single side-effect with most impact, affecting 90% of post-surgical adjuvant radiotherapy of women with breast cancer[346]. Skin reactions, pain, and sleeping difficulties also highly impacted participants and increased in prevalence over the 6-month treatment period.

*Chemotherapy*

Anthracyclines are a class of drug used in chemotherapy; however, their use is limited by its dose-dependent cardiotoxicity[347]. The underlying mechanism of anthracycline-induced myocardial damage has been attributed to multiple adverse effects on cardiomyocytes by free radical production[348]. Cardiomyopathy and heart failure are the most common clinical manifestations of anthracycline cardiotoxicity[349]. In a retrospective analysis of 630 patients randomized to doxorubicin plus placebo in three phase III studies by Swain et al.[350], the percentage of patients with doxorubicin-induced heart failure was 5 at a cumulative dose of 400mg/m$^2$, 26 at a dose of 550mg/m$^2$ and 48 at a dose of 700 mg/m$^2$. The cardiotoxic effect of epirubicin becomes common at higher cumulative doses than with doxorubicin[308].

Population-based data on hospitalization rate for toxicity from breast cancer chemotherapy showed that among 35,060 older women diagnosed with breast cancer, more than 9% were admitted with neutropenia, fever, thrombocytopenia, or adverse effect from systemic therapy compared to 0.5% of women with breast cancer who did not receive chemotherapy[351]. Considering this data was collected from 1991 to 1996, medications that treat the adverse effects of chemotherapy were less available than they are today. A more recent study[352] from 2006 recorded

the frequency of adverse effects in breast cancer chemotherapy recipients and found the percentages of those who were hospitalized or visited the emergency room during their chemotherapy treatment was 8.4% for fever or infection, 5.5% for neutropenia or thrombocytopenia, 2.5% for dehydration or electrolyte disorders, 2.4% for nausea, emesis, or diarrhea, 2.2% for anemia, 2% for constitutional symptoms, 2.3% for deep vein thrombosis or pulmonary embolus, and 0.9% for malnutrition.

*Hormone Therapy*

Despite proven benefits of tamoxifen, its use is often limited by side-effects such as hot flashes (64%), vaginal dryness (35%), sleep problems (36%), weight gain (6%) and depression, irritability, or mood swings (6%)[353]. Fisher et al.[312] found at least 10% difference in the number of tamoxifen patients compared to placebo patients experiencing hot flashes (69.6% vs. 59.0%) and vaginal discharge (32.4% vs. 20.0%). Yet, recent results from the International Breast Cancer Intervention suggest that women may mistakenly attribute age-related menopausal symptoms to side-effects of the drug[354].

Treatment with aromatase inhibitors can cause osteoporosis, as well as myalgia and arthralgia[355]. Joint discomfort, which was rated between mild and moderate in 92% of patients, has been observed to begin appearing at approximately 2 months after the start of treatment and peak at around the 6-month mark[356]. Cardiac events, such as myocardial infarction have been reported at low frequency in trials comparing aromatase inhibitor use to control of 5 years of tamoxifen[319]. One meta-analysis found a low absolute risk of around 0.5% with aromatase inhibitor use[357].

*Targeted Therapy*

Although targeted therapies are considered less toxic and better tolerated by patients compared with traditional chemotherapy agents, rare but serious complications have been described[319]. Efficacy and safety of recombinant humanized anti-HER2 monoclonal antibody was evaluated in 222 women with metastatic breast cancer that had progressed after chemotherapy[320]. After a median duration of 9.1 months of therapy, the most common adverse event (40% of patients) was infusion-associated fever and/or chills of mild to moderate severity that mostly occurred during the first infusion. The most clinically significant adverse event was cardiac dysfunction, occurring in 4.7% of patients and only 1% of patients discontinued the study because of treatment-related side-effects. Other studies have noted cardiomyopathy and congestive heart failure[319].

Lapatinib can cause severe diarrhea and this was the most frequent adverse event in a study of lapatinib monotherapy[325]. Additionally, 98.4% of these subjects experienced at least one adverse event; although, most were Grade 1 or 2 in severity. In another study, the incidence of Grade ≥2 diarrhea was 13.2% and Grade 1-2 diarrhea was 23.7%[358]. Unlike chemotherapy, trastuzumab did not have toxic effects such as nausea, vomiting, hair loss, and bone marrow toxicity, yet neutropenia, leukopenia, and fatigue have been cited as common[359].

**Evidence-Based Exercise**

Exercise is increasingly being recognized as an effective strategy to counter the adverse effects of cancer therapy[349,360]. Effectiveness of exercise interventions in cancer patients and survivors has been assessed in both qualitative systematic reviews and meta-analyses that included various types of cancers and trial designs[349,361–363]. Data from 82 studies, majority of which included female breast cancer patients, suggests many health benefits from physical activity during

and post cancer treatments, including positive effects on upper and lower body strength, fatigue, aerobic fitness, functional quality of life, anxiety, self-esteem, and breast cancer-specific concerns[362].

An important issue in oncology is to evaluate quality of life in cancer patients[364]. While adjuvant chemotherapy for breast cancer reduces the risk of cancer recurrence and death, it also negatively impacts patients' quality of life[360,363]. Literature shows that physical activity is positively associated with breast cancer general well-being[360,365,366]. Overall quality of life in both physical and social functioning domains increased significantly by 9.1 points in the exercise group of 53 postmenopausal breast cancer survivors, whose training consisted of cycling three times per week for 15 weeks[365].

Physical activity guidelines for breast cancer patients continue to recommend both aerobic and resistance exercise[367–369]. The START trial[360] performed in Canada between 2003 and 2005 randomly assigned 242 breast cancer patients initiating adjuvant chemotherapy to usual care (n = 82), supervised resistance exercise (n = 78), or supervised aerobic exercise (n = 82) for the duration of their chemotherapy. Aerobic exercise was superior to usual care for improving self-esteem, aerobic fitness, and percent body fat, while resistance exercise was more effective than usual care for improving self-esteem, muscular strength, lean body mass, and chemotherapy completion rate. Another study found the standard dose aerobic group, high dose aerobic group, and combined (aerobic and resistance) dose group were all equally beneficial towards chemotherapy-treated breast cancer subjects' physical functioning assessments[368]. It is becoming more apparent that cardiorespiratory fitness is a parameter of critical importance following a breast cancer diagnosis and exercise guidelines include an emphasis on this component of health (Table 5).

**Table 5 FITT Formula for Breast Cancer Patients**[370–372]

| | Aerobic | Resistance | Flexibility |
|---|---|---|---|
| **F** | 3-5 d/wk | 2-3 d/wk | 2-7 d/wk |
| **I** | ≥70% $VO_{2peak}$ or 40-60% HRR or RPE 4-8 | 10-15 reps | Hold 10-15 sec |
| **T** | 20-60 min/day or 150 min/wk | 2 sets at perfect form, progress to 3 sets | 3-4 reps or ≥10 min/d |
| **T** | Running, cycling, swimming, stair climbing | Circuit training, body weight, free weights, dancing, agility (ladder, single leg balance) | Controlled dynamic stretch, yoga, Tai chi |

$VO_{2peak}$ = peak oxygen uptake
HRR = heart rate reserve
RPE = rate of perceived exertion

A median follow-up of 89 months from the START study further investigated whether exercise during adjuvant chemotherapy may improve several efficacy end points[373]. Eight-year disease free survival was 82.7% for the exercise groups compared with 75.6% for the control group, and stronger effects were observed for overall survival, distant disease-free survival, and recurrence-free interval.

Although arthralgia has been experienced in up to 50% of breast cancer survivors treated with aromatase inhibitors, RCTs continue to show the beneficial effect of resistance exercise towards this debilitating side-effect[374]. The HOPE study[375] examined the impact of an exercise intervention on severity of aromatase inhibitor-induced joint pain. After 12 months of resistance training, worst joint pain scores decreased by 29% compared to controls whose scores instead increased by 3%. Pain severity scores on multiple questionnaires decreased significantly in the exercise group compared to those receiving no exercise.

Breast cancer-related lymphedema, often a result of surgery and/or radiation therapy[336], remains a frequent complication among survivors[376]. While previous recommendations have been

to avoid lifting with the affected arm following treatment[377] mainly due to concern for increasing the onset of lymphedema symptoms[360,378], several studies have shown a myriad of benefits. Breast cancer patients who performed resistance exercises were less likely to experience arm swelling and other lymphedema symptoms[376,379], had reduced need for therapist-delivered treatment (by 50%)[379], greater muscle strength and endurance, and improved quality of life compared to controls[380].

**Adverse Effects to Exercise**

Many meta-analyses and RCTs report no significant adverse effects of physical activity interventions among breast cancer patients, stating exercise to be a safe and well-tolerated alternative to drug therapy[360,362,368,379–381]. One RCT[378] reported injuries to the back (n=4), wrist (n=1), lower leg and ankle (n=5), rotator cuff (n=1), and shoulder tendonitis (n=1), while another noted worsening of fatigue (n=2)[382]. As cancer therapies are regularly changing, fitness coaches need to understand the patient's diagnosis and treatment plan in order to evaluate their exercise tolerance and recommend a safe and effective exercise program. Changes resulting from popular therapies that may affect body systems relevant to physical activity may include worsened bone health, fatigue, pain, cardiovascular changes, musculoskeletal soft tissue changes, and impaired immune system[376].

The RENEW study[383] that included a home-based diet and exercise intervention for older, overweight long-term cancer survivors, including breast cancer reported a total of 201 adverse events, with only 5 directly attributable to exercise. These included increased blood pressure, hip pain, pulled hamstring, fall, and calf pain. However, there were no differences between the intervention and control groups in the total number of events, or in events in any subcategory.

Study participants were not noted to have been supervised by a trained exercise therapist during their exercise sessions, which is recommended for cancer patients[369].

## COST ANALYSIS

In Canada, prescription drugs cost upwards of $29 billion per year, the second most costly component of health care[384]. A report by Kolber and colleagues[385] listed various prescription drugs for chronic medical conditions and their costs based on coverage by Alberta Blue Cross. The annual cost of several of these medications relating to HTN, T2DM, osteoporosis, depression and breast cancer are listed in a modified table below (Table 6) and are compared to the yearly cost of various types of gym memberships. Not included in Table 6 are physical activities that are readily accessible and have no cost, such as running outdoors or stair climbing.

**Table 6 Annual Cost of Prescription Medications and Gym Memberships**

| Condition | Drug Class | Type | Brand Name | Dosing | Annual Cost[ψ] |
|---|---|---|---|---|---|
| Hypertension | β-blocker | Atenolol | Tenormin | 50mg | $100 |
| | Diuretic | Cholithalodone | Hygroton | 50mg | $60 |
| | ACEI | Ramipril | Altace | 5mg, 10mg | $120 |
| Osteoporosis | Bisphosphonate | Alendronate | Fosamax | 70mg once weekly | $180 |
| | | Risedronate | Actonel | 35mg once weekly | $180 |
| Breast Cancer | Hormone therapy | Tamoxifen | | | $480-600[ø] |
| Depression | SSRI | Sertraline | Zoloft | 50mg | $200 |
| | SNRI | Duloxetine | Cymbalta | 30mg | $800 |
| Diabetes | Biguanides | Metformin | Glucophage | 500mg | $120 |
| | Insulin therapy | Regular Insulin | Novolin Toronto/ Humulin R | 100U/mL | $240 |
| **Gym Membership** | | | | | |
| Kerrisdale Community Centre | | | | | $168-221[ε] |
| UBC BodyWorks | | | | | $415 |
| Steve Nash Fitness World | | | | | $540-900 |
| YMCA | | | | | $588-732 |
| Personal training[t] | | | | | $7,056 |

[ψ] based on coverage by Alberta Blue Cross [385]

[ø] based on Ontario Ministry of Health and Long-Term Care [386]

[ε] not including $5-8 community centre membership fee

[t] based on YMCA pricing $49/session, 3x/wk

*Note*. Data for Kerrisdale Community Centre from http://www.kerrisdalecc.com/facilities-rentals/exercise-room/, for UBC BodyWorks from http://outreach-prog.sites.olt.ubc.ca/files /2013/10/Fall-2017-BW-Brochure.pdf, for Steve Nash Fitness World from https://www.snclubs.com/join, and for YMCA and personal training from https://gv.ymca.ca/Join-the-YMCA/How-to-Join-Robert-Lee-YMCA.

## CONCLUSION

In this review, five chronic diseases along with their commonly prescribed pharmacological therapies are compared against exercise therapy with respect to their positive and negative impact on the body. These are drugs that are prescribed to improve specific conditions, but in many cases, they have significant adverse effects on other areas of health. Many individuals do not respond adequately to drug therapy or withdraw use due to side-effects, which may further provoke health professionals to prescribe additional drugs to treat the side-effects from the originally prescribed medication. The concern of polypharmacy is especially common in elderly patients. There is irrefutable evidence of the effectiveness of regular physical activity for chronic disease management and treatment, as well as mitigating common side effects of drug therapy. Furthermore, unlike many of the approved pharmaceutical drugs, research has shown little side effect to proper exercise therapy. Primary care physicians should include exercise when designing treatment and management plans for patients. Even though regular exercise induces similar remedial physiological effects in the body as pharmaceuticals for chronic disease populations, the concept of ‘exercise as medicine’ is seldom applied with enough clout. Exercise is in fact powerful medicine.

## REFERENCES


1. National Center for Chronic Disease Prevention and Health Promotion CDC. CHAPTER 3: Physiologic Responses and Long-Term Adaptations to Exercise. *Phys. Act. Heal. A Rep. Surg. Gen.* 61–77 (1999).
2. Durstine, J. L., Gordon, B., Wang, Z. & Luo, X. Chronic disease and the link to physical activity. *J. Sport Heal. Sci.* **2,** 3–11 (2013).
3. Kimberly Elmslie. Against the Growing Burden of Disease: Protecting Canadians from Illness. *Public Heal. Agency Canada* (2012).
4. Hanghøj, S. & Boisen, K. A. Self-reported barriers to medication adherence among chronically ill adolescents: A systematic review. *J. Adolesc. Heal.* **54,** 121–138 (2014).
5. Hansson, L. *et al.* Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* **356,** 359–365 (2000).
6. Booth, F. W., Roberts, C. K. & Laye, M. J. Lack of exercise is a major cause of chronic diseases. *Compr. Physiol.* **2,** 1143–1211 (2012).
7. Statistics Canada. *Distribution of the household population meeting/not meeting the Canadian physical activity guidelines, by sex and age group, occaisional (percentage)*. (2015).
8. Kruk, J. Physical activity in the prevention of the most frequent chronic diseases: An analysis of the recent evidence. *Asian Pacific J. Cancer Prev.* **8,** 325–338 (2007).
9. Warburton, D. E. R., Nicol, C. W. & Bredin, S. S. D. Health benefits of physical activity: the evidence. *CMAJ* **174,** 801–9 (2006).
10. Forouzanfar, M. H. *et al.* Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. *Jama* **317,** 165 (2017).
11. Benjamin, E. J. *et al. Heart Disease and Stroke Statistics 2017 Update: A Report From the American Heart Association*. *Circulation* (2017). doi:10.1161/CIR.0000000000000485
12. Moore, J. Hypertension: catching the silent killer. *Nurse Pract.* **30,** 16–18, 23–24, 26-27-37 (2005).
13. Lilley, L. L. & Guanci, R. Getting back to basics. *Am J Nurs* **94,** 15–6. (1994).
14. Kantor, E. D., Rehm, C. D., Haas, J. S., Chan, A. T. & Giovannucci, E. L. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *Jama* **314,** 1818 (2015).
15. Sica, D. A. Combination Calcium Channel Blocker Therapy in the Treatment of Hypertension. *J. Clin. Hypertens.* **3,** (2001).
16. Skolnik, N. S., Beck, J. D. & Clark, M. Combination antihypertensive drugs: recommendations for use. *Am. Fam. Physician* **61,** 3049–56 (2000).

17. Ram, C. V. S. Angiotensin Receptor Blockers: Current Status and Future Prospects. *Am. J. Med.* **121,** 656–663 (2008).

18. Sudhakar, R., George, M. K., Yasaswini, B., Sundararajan, N. & Mariyam, A. S. Adverse drug reaction associated with anti hypertensive drugs and its management. *Int. J. Pharm. Sci. Res.* **7,** 898–905 (2016).

19. Davies, M. K., Gibbs, C. R. & Yip, G. Y. H. ABC of heart failure: Management: Diuretics, ACE inhibitors, and nitrates. *Br. Med. J.* **320,** 428–431 (2000).

20. Heran, B. S., Wong, M. M. Y., Heran, I. K. & Wright, J. M. Blood pressure lowering efficacy of angiotensin converting enzyme ( ACE ) inhibitors for primary hypertension ( Review ) Blood pressure lowering efficacy of angiotensin converting enzyme ( ACE ) inhibitors for primary hypertension. *Cochrane Libr.* 2008–2010 (2009). doi:10.1002/14651858.CD003823.pub2.Copyright

21. Taylor, A. A., Siragy, H. & Nesbitt, S. Angiotensin Receptor Blockers: Pharmacology, Efficacy, and Safety. *J. Clin. Hypertens.* **13,** 677–686 (2011).

22. Heran, B. S., Wong, M. M. Y., Heran, I. K. & Wright, J. M. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst. Rev.* (2008). doi:10.1002/14651858.CD003822.pub2

23. Larochelle, P., Tobe, S. W. & Lacourcière, Y. β-Blockers in hypertension: Studies and meta-analyses over the years. *Can. J. Cardiol.* **30,** 16–22 (2014).

24. Wong, W. K. A systematic review of the blood pressure lowering efficacy. (University of British Columbia, 2014).

25. British Hypertension Society. *Beta-adrenorecptor antagonists (beta-blockers)*. (2008). http://bhsoc.org/resources/therapeutics/

26. British Hypertension Society. *Thiazide and thiazide-like diuretics*. *British Hypertension Society* (2008). http://bhsoc.org/resources/therapeutics/

27. Blowey, D. L. Diuretics in the treatment of hypertension. *Pediatr. Nephrol.* **31,** 2223–2233 (2016).

28. James, P. A. *et al.* 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. *Jama* **311,** 507 (2014).

29. Musini, V. M., Nazer, M., Bassett, K. & Wright, J. M. Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension ( Review ) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. *Cochrane Libr.* (2014).

30. Elliott, W. J. & Ram, C. V. S. Calcium channel blockers. *J. Clin. Hypertens.* **13,** 687–689 (2011).

31. British Hypertension Society. *Calcium Channel Blockers (CCBs)*. *British Hypertension Society* (2008). http://bhsoc.org/resources/therapeutics/

32. Bucci, C., Mamdani, M. M., Juurlink, D. N. & Tu, J. V. Dihydropyridine calcium channel blockers and cardiovascular outcomes in elderly patients: a population-based study. *Can.*

*J. Cardiol.* **24,** 629–32 (2008).

33. Mon, M. & Wong, Y. A systematic review of the blood pressure loweing efficacy of calcium channel blockers in the treatment of primary hypertension. (University of British Columbia, 2007).

34. Law, M. R. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *Bmj* **326,** 1427 (2003).

35. Wald, D. S., Law, M., Morris, J. K., Bestwick, J. P. & Wald, N. J. Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 Participants from 42 Trials. *Am. J. Med.* **122,** 290–300 (2009).

36. Chen, J. M. H., Heran, B. S., Perez, M. I. & Wright, J. M. Blood pressure lowering efficacy of beta-blockers as second- line therapy for primary hypertension ( Review ). *Cochrane Database Syst. Rev.* 2–4 (2010). doi:10.1002/14651858.CD007185.pub2.Copyright

37. British Hypertension Society. *Angiotensin converting enzyme (ACE) inhibitors*. *British Hypertension Society* (2008). http://bhsoc.org/resources/therapeutics/

38. Israili, Z. . & Hall, W. D. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. *Ann. Intern. Med.* **117,** 234–242 (1992).

39. Bangalore, S. *et al.* Antihypertensive drugs and risk of cancer: Network meta-analyses and trial sequential analyses of 324 168 participants from randomised trials. *Lancet Oncol.* **12,** 65–82 (2011).

40. Al Sabbah, Z., Mansoor, A. & Kaul, U. Angiotensin receptor blockers - Advantages of the new sartans. *J. Assoc. Physicians India* **61,** 464–470 (2013).

41. Rasmussen, E. R., Mey, K. & Bygum, A. Angiotensin-converting enzyme inhibitor-induced angioedema - A dangerous new epidemic. *Acta Derm. Venereol.* **94,** 260–264 (2014).

42. Sipahi, I., Debanne, S. M., Rowland, D. Y., Simon, D. I. & Fang, J. C. Angiotensin-receptor blockade and risk of cancer: Meta-analysis of randomised controlled trials. *Lancet Oncol.* **11,** 627–636 (2010).

43. Yoon, C., Yang, H. S., Jeon, I., Chang, Y. & Park, S. M. Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and cancer risk: A meta-analysis of observational studies. *Cmaj* **183,** (2011).

44. Zhao, Y.-T., Li, P.-Y., Zhang, J.-Q., Wang, L. & Yi, Z. Angiotensin II Receptor Blockers and Cancer Risk. *Medicine (Baltimore).* **95,** e3600 (2016).

45. Ko, D. T. *et al.* Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *Jama* **288,** 351–7 (2002).

46. Messerli, F. H., Bangalore, S. & Grossman, E. Adverse effects and tolerability of β blockers. *BMJ* **353,** 3142 (2016).

47. Bradley, H. a, Wiysonge, C. S., Volmink, J. a, Mayosi, B. M. & Opie, L. H. How strong is

the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis. *J. Hypertens.* **24,** 2131–41 (2006).

48. Bangalore, S., Messerli, F. H., Kostis, J. B. & Pepine, C. J. Cardiovascular Protection Using Beta-Blockers. A Critical Review of the Evidence. *J. Am. Coll. Cardiol.* **50,** 563–572 (2007).

49. Roberts, C. & Barritt, W. Raynaud's phenomenon as side effect of beta-blockers in hypertension. *Br. Med. J.* **31,** 1498–1499 (1976).

50. Mohokum, M., Hartmann, P. & Schlattmann, P. The association of Raynaud syndrome with β-blockers: a meta-analysis. *Angiology* **63,** 535–40 (2012).

51. Sharma, A. M., Pischon, T., Hardt, S., Kunz, I. & Luft, F. C. Beta-Adrenergic Receptor Blockers and Weight Gain. *Pima* 250–254 (2001).

52. Kumpusalo, E., Parnanen, H. & Takala, J. Side effects of beta-blocker treatment for hypertension. *Scand. J. Prim. Health Care* **18,** 127–128 (2000).

53. Sica, D. A., Carter, B., Cushman, W. & Hamm, L. Thiazide and loop diuretics. *J. Clin. Hypertens.* **13,** 639–643 (2011).

54. Wright, J. M. & Musini, V. M. First-line drugs for hypertension (Review). *Cochrane Libr.* (2009). doi:10.1002/14651858.CD001841.pub2.www.cochranelibrary.com

55. Clayton, J. A., Rodgers, S., Blakey, J., Avery, A. & Hall, I. P. Thiazide diuretic prescription and electrolyte abnormalities in primary care. *Br. J. Clin. Pharmacol.* **61,** 87–95 (2006).

56. Chrysant, S. G., Melino, M., Karki, S., Lee, J. & Heyrman, R. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin. Ther.* **30,** 587–604 (2008).

57. Makani, H. *et al.* Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate – a meta-analysis of randomized trials. *J. Hypertens.* **29,** 1270–1280 (2011).

58. Li, C. I. *et al.* Use of Antihypertensive Medications and Breast Cancer Risk Among Women Aged 55 to 74 Years. *JAMA Intern. Med.* **173,** 1629 (2013).

59. Wang, A. & Manson, J. E. Hypertension: Do calcium-channel blockers increase breast cancer risk? *Nat. Rev. Cardiol.* **10,** 68–77 (2013).

60. Mallat, S. G., Itani, H. S. & Tanios, B. Y. Current perspectives on combination therapy in the management of hypertension. *Integr. Blood Press. Control* **6,** 69–78 (2013).

61. Florez, J. C. *et al.* New England Journal. *Group* 241–250 (2006). doi:10.1056/NEJMoa1109071

62. Messerli, F. H., Bangalore, S. & Julius, S. Risk/benefit assessment of-blockers and diuretics precludes their use for first-line therapy in hypertension. *Circulation* **117,** 2706–2715 (2008).

63. Doumas, M. & Douma, S. The effect of antihypertensive drugs on erectile function: a proposed management algorithm. *J Clin Hypertens.(Greenwich)* **8,** 359–364 (2006).

64. Fung, V., Huang, J., Brand, R., Newhouse, J. P. & Hsu, J. Hypertension treatment in a medicare population: Adherence and systolic blood pressure control. *Clin. Ther.* **29,** 972–984 (2007).

65. Gradman, A. H., Basile, J. N., Carter, B. L. & Bakris, G. L. Combination Therapy in Hypertension. *J. Clin. Hypertens.* **13,** 146–154 (2011).

66. Cornelissen, V. A. & Smart, N. A. Exercise training for blood pressure: a systematic review and meta-analysis. *J. Am. Heart Assoc.* **2:e004473,** (2013).

67. Fagard, R. H. Exercise characteristics and the blood pressure response to dynamic physical training. *Med. Sci. Sports Exerc.* **33,** S484–S492 (2001).

68. Dinenno, F. A. *et al.* Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. *J. Physiol.* **534,** 287–295 (2001).

69. Cornelissen, V. A. & Fagard, R. H. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension* **46,** 667–675 (2005).

70. Hermann, M., Flammer, A. & Lscher, T. F. Nitric Oxide in Hypertension. *J. Clin. Hypertens.* **8,** 17–29 (2006).

71. Higashi, Y. & Yoshizumi, M. Exercise and endothelial function: Role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients. *Pharmacol. Ther.* **102,** 87–96 (2004).

72. Roque, F. R., Hernanz, R., Salaices, M. & Briones, A. M. Exercise training and cardiometabolic diseases: Focus on the vascular system. *Curr. Hypertens. Rep.* **15,** 204–214 (2013).

73. Korsager Larsen, M. & Matchkov, V. V. Hypertension and physical exercise: The role of oxidative stress. *Medicina (B. Aires).* **52,** 19–27 (2016).

74. Pescatello, L. S. *et al.* Exercise and hypertension. *Aust. Fam. Physician* **34,** 419–424 (2004).

75. Dinenno, F. a *et al.* Age-associated arterial wall thickening is related to elevations in sympathetic activity in healthy humans Age-associated arterial wall thickening is related to elevations in sympathetic activity in healthy humans. *Am J Physiol Hear. Circ Physiol* **278,** H1205–H1210 (2000).

76. Nunez, B. D. *et al.* Comparison of diastolic left ventricular filling and cardiac dysrhythmias in hypertensive patients with and without isolated septal hypertrophy. *Am. J. Cardiol.* **74,** 585–589 (1994).

77. Lavie, C. J. & Milani, R. V. Effects of cardiac rehabilitation, exercise training, and weight reduction on exercise capacity, coronary risk factors, behavioural characteristics, and quality of life in obese coronary patients. *J. Am. Coll. Cardiol.* **79,** 397–401 (1997).

78. Lavie, C. J., Ventura, H. O. & Messerli, F. H. Hypertension, obesity, left ventricular hypertrophy, complex ventricular ectopic activity, and increased risk for sudden death. *J. Cardiopulm. Rehabil.* **13,** 264–270 (1993).

79. Rinder, M. R. *et al.* Comparison of effects of exercise and diuretic on left ventricular geometry, mass, and insulin resistance in older hypertensive adults. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **287,** R360-8 (2004).

80. Leung, A. A. *et al.* Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. *Can. J. Cardiol.* **33,** 557–576 (2017).

81. Quinn, U., Tomlinson, L. A. & Cockcroft, J. R. Arterial stiffness. *JRSM Cardiovasc. Dis.* **1,** 1–8 (2012).

82. Kim, D. & Ha, J.-W. Hypertensive response to exercise: mechanisms and clinical implication. *Clin. Hypertens.* **22,** 17 (2016).

83. Pescatello, L. S. *et al.* Assessing the Existing Professional Exercise Recommendations for Hypertension: A Review and Recommendations for Future Research Priorities. *Mayo Clin. Proc.* **90,** 801–812 (2015).

84. Exercise is Medicine. *Exercising with High Blood Pressure*. (2013). http://www.exerciseismedicine.org/support_page.php/your-rx-for-health-series/

85. Sigal, R. J., Kenny, G. P., Wasserman, D. H. & Castaneda-Sceppa, C. Physical activity/exercise and type 2 diabetes. *Diabetes Care* **27,** 2518–2539 (2004).

86. Centers for Disease Control and Prevention. National Diabetes Statistics Report , 2014 Estimates of Diabetes and Its Burden in the Epidemiologic estimation methods. *US Dep. Heal. Hum. Serv.* 2009–2012 (2014).

87. Virally, M. *et al.* Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives. *Diabetes Metab.* **33,** 231–244 (2007).

88. Appuhamy, J. A. D. R. N. *et al.* Effects of diet and exercise interventions on diabetes risk factors in adults without diabetes: meta-analyses of controlled trials. *Diabetol. Metab. Syndr.* **6,** 127 (2014).

89. Gordon, L. *et al.* Changes in clinical and metabolic parameters after exercise therapy in patients with type 2 diabetes. *Arch Med Sci* **4,** 427–437 (2008).

90. Viollet, B. *et al.* Cellular and molecular mechanisms of metformin: an overview. *Clin. Sci.* **122,** 253–270 (2012).

91. Pernicova, I. & Korbonits, M. PerMetformin-mode of action and clinical implications for diabetes and cancer. *Natl. Rev. Endocrinol.* **10,** 143–156 (2014).

92. Sherifali, D., Nerenberg, K., Pullenayegum, E., Cheng, J. E. & Gerstein, H. C. The Effect of Oral Antidiabetic Agents on A1C Levels. *Diabetes Care* **33,** 1859–1864 (2010).

93. Hundal, R. S. & Inzucchi, S. E. Metformin: New understandings, new uses. *Drugs* **63,** 1879–1894 (2003).

94. Sirtori, C. R. & Pasik, C. Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. *Pharmacol. Res.* **30,** 187–228 (1994).

95. Chen, J. & Smerdely, P. Hypocalcaemia after denosumab in older people following fracture. *Osteoporos. Int.* **28,** 517–522 (2017).

96. Thulé, P. M. & Umpierrez, G. Sulfonylureas: a new look at old therapy. *Curr. Diab. Rep.* **14,** 473 (2014).

97. Daskalopoulou, S. S. *et al.* The 2015 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can. J. Cardiol.* **31,** 549–568 (2015).

98. Brunetti, L. & Kalabalik, J. Management of type-2 diabetes mellitus in adults: focus on individualizing non-insulin therapies. *P T* **37,** 687–96 (2012).

99. Proks, P., Reimann, F., Green, N., Gribble, F. & Frances, A. Sulfonylurea stimulation of insulin secretion. *Am. Diabetes Assoc.* **51,** 368–377 (2002).

100. Zhang, A. C. *et al.* Target of Antidiabetic Sulfonylurea Drugs. **325,** 607–610 (2017).

101. Hinke, S. a. Epac2: a molecular target for sulfonylurea-induced insulin release. *Sci. Signal.* **2,** pe54 (2009).

102. Lingvay, I., Kaloyanova, P. F., Adams-Huet, B., Salinas, K. & Raskin, P. Insulin as Initial Therapy in Type 2 Diabetes. *J. Investig. Med.* **55,** 62–68 (2007).

103. Nasri, H. & Kopaei, M. R. Metformin : Current knowledge. *J. Res. Med. Sci.* **19,** 658–664 (2017).

104. Philbreck, A. M., Ernst, M. E., McDanel, D. L., Ross, M. B. & Moores, K. G. Metformin use in renal dysfunction: Is a serum creatinine threshold appropriate? *Am. J. Heal. Pharm.* **66,** 2017–23 (2009).

105. Inzucchi, S. E., Lipska, K. J., Mayo, H., Bailey, C. J. & McGuire, D. K. Metformin in Patients With Type 2 Diabetes and Kidney Disease. *Jama* **312,** 2668 (2014).

106. Bodmer, M., Meier, C., Krähenbühl, S., Jick, S. S. & Meier, C. R. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia a nested case-control analysis. *Diabetes Care* **31,** 2086–2091 (2008).

107. Boucaud-Maitre, D. *et al.* Lactic acidosis: relationship between metformin levels, lactate concentration and mortality. *Diabet. Med.* **33,** 1536–1543 (2016).

108. Greenhill, C. Diabetes: Metformin and the risk of dialysis. *Nat. Rev. Endocrinol.* **12,** 2016 (2016).

109. Carlson, N. *et al.* Metformin-associated risk of acute dialysis in patients with type 2 diabetes: A nationwide cohort study. *Diabetes, Obes. Metab.* **18,** 1283–1287 (2016).

110. Soranna, D. *et al.* Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist* **17,** 813–822 (2012).

111. Petznick, A. Insulin management of type 2 diabetes mellitus. *Am. Fam. Physician* **84,**

183–190 (2011).

112. Zammitt, N. . & Frier, B. M. Hypoglycemia in Type 2 Diabetes. *Diabetes Care* **28,** 2948 (2005).

113. UKPDS Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* **352,** 837–853 (1998).

114. Yang, Z., Scott, C. A., Mao, C., Tang, J. & Farmer, A. J. Resistance exercise versus aerobic exercise for type 2 diabetes: A systematic review and meta-analysis. *Sport. Med.* **44,** 487–499 (2014).

115. Karve, A. & Hayward, R. A. Prevalence , diagnosis , and treatment of impaired fasting glucose and impaired glucose tolerance in nondiabetic US adults. *Diabetes Care* **33,** 2355 (2010).

116. Meigs, J. B. Multiple biomarker prediction of type 2 diabetes. *Diabetes Care* **32,** 1346–1348 (2009).

117. Cheekurthy, A. J. Biochemical Biomarkers-Independent Predictors of Type 2 Diabetes Mellitus. *J. Bioanal. Biomed.* **7,** 35–39 (2015).

118. Zou, Z., Cai, W., Cai, M., Xiao, M. & Wang, Z. Influence of the intervention of exercise on obese type II diabetes mellitus: A meta-analysis. *Prim. Care Diabetes* **10,** 186–201 (2016).

119. Goldenberg, R. & Punthakee, Z. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. *Can. J. Diabetes* **37,** 8–11 (2013).

120. Khaw, K. T. *et al.* Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ* **322,** 15–8 (2001).

121. Boule, N. G., Haddad, E., Kenny, G. P., Wells, G. A. & Sigal, R. J. Effects of Exercise on Glycemic Control and Body Mass in Type 2 Diabetes Mellitus A Meta-analysis of Controlled Clinical Trials. **286,** 11–15 (2011).

122. Umpierre, D. *et al.* Physical Activity Advice Only or Structured exercise training and association With HbA 1c Levels in Type 2 Diabetes. *JAMA J. Am. Med. Assoc.* **305,** 1790–1799 (2011).

123. Jae, S. Y. *et al.* Effects of lifestyle modifications on C-reactive protein: contribution of weight loss and improved aerobic capacity. *Metabolism.* **55,** 825–831 (2006).

124. Hayashino, Y., Mashitani, T., Tsujii, S. & Ishii, H. Elevated levels of hs-crp are associated with high prevalence of depression in japanese patients with type 2 diabetes: The diabetes distress and care registry at tenri (DDCRT 6). *Diabetes Care* **37,** 2459–2465 (2014).

125. Ma, Y. *et al.* Association between dietary fiber and serum C-reactive protein-. *Am. J. Clin. Nutr.* **83,** 760–766 (2006).

126. Pfutzner, A. & Forst, T. High-sensitivity c-reactive protein as cardiovascular risk marker

in patients with diabetes mellitus. *Diabetes Technol. Ther.* **8,** 28–37 (2006).

127. Bahceci, M. *et al.* Is serum c-reactive protein concentration correlated with HbA1c and insulin resistance in type 2 diabetic men with or without coronary heart disease? *J. Endocrinol. Invest.* **28,** 145–150 (2005).

128. Kim, K. B. Effect of different training mode on Interleukin-6 (IL-6) and C-reactive protein (CRP) in type 2 diabetes mellitus (T2DM) patients. *J Exerc Nutr. Biochem* **18,** 371–378 (2014).

129. Kadoglou, N. P. E. *et al.* The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. *Eur. J. Cardiovasc. Prev. Rehabil.* **14,** 837–843 (2007).

130. Di Fenza, R. & Fiorina, P. Physical Activity and Inflammation. in *Cellular Physiology and Metabolism of Physical Exercise* Ch. 10 (2012).

131. Pischon, T., Hankinson, S. E., Hotamisligil, G. S., Rifai, N. & Rimm, E. B. Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory markers. *Obes. Res.* **11,** 1055–64 (2003).

132. Pedersen, B. K. Exercise and cytokines. *Immunol. Cell Biol.* **78,** 532–535 (2000).

133. Thomas, D., Elliott, E. J. & Naughton, G. A. Exercise for type 2 diabetes mellitus (Review). *Cochrane Libr.* (2009).

134. Care, D. Changes in Physical Fitness Predict Improvements in Modifiable Cardiovascular Risk Factors Indepe ... (2012).

135. Pedersen, B. K. & Saltin, B. Exercise as medicine - Evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand. J. Med. Sci. Sport.* **25,** 1–72 (2015).

136. Huang, L.-H., Liao, Y.-L. & Hsu, C.-H. Waist circumference is a better predictor than body mass index of insulin resistance in type 2 diabetes. *Obes. Res. Clin. Pract.* **6,** e314–e320 (2012).

137. Luo, W. *et al.* 2 Years Change of Waist Circumference and Body Mass Index and Associations With Type 2 Diabetes Mellitus in Cohort Populations. *Obes. Res. Clin. Pract.* **7,** e290–e296 (2013).

138. Lee, S. *et al.* Role of Exercise in Reducing the Risk of Diabetes and Obesity Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without Type 2 diabetes. *J. Appl. Physiol.* **6,** 1220–1225 (2005).

139. Lewis, G. D. *et al.* Metabolic Signatures of Exercise in Human Plasma. *Sci. Transl. Med.* **2,** 33ra37-33ra37 (2010).

140. Wei, M., Gibbons, L. W., Kampert, J. B., Nichaman, M. Z. & Blair, S. N. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann. Intern. Med.* **132,** 605–11 (2000).

141. Lessard, S. J. *et al.* Impaired skeletal muscle β-adrenergic activation and lipolysis are associated with whole-body insulin resistance in rats bred for low intrinsic exercise capacity. *Endocrinology* **150,** 4883–4891 (2009).

142. Sigal, R. J., Kenny, G. P., Wasserman, D. H., Castaneda-Sceppa, C. & White, R. D. Physical activity/exercise and type 2 diabetes: A consensus statement from the American Diabetes Association. *Diabetes Care* **29,** 1433–1438 (2006).

143. Snowling, N. J. & Hopkins, W. G. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients. *Diabetes Care* **29,** 2518–2527 (2006).

144. Pedersen, B. K. & Saltin, B. Evidence for prescribing exercise as therapy in chronic disease. *Scand. J. Med. Sci. Sports* **16 Suppl 1,** 3–63 (2006).

145. Herriott, M. T., Colberg, S. R., Parson, H. K., Nunnold, T. & Vinik, A. I. Effects of 8 weeks of flexibility and resistance training in older adults with type 2 diabetes. *Diabetes Care* **27,** 2988–2989 (2004).

146. Albright, A. *et al.* American College of Sports Medicine position stand. Exercise and type 2 diabetes. *Med. Sci. Sports Exerc.* **32,** 1345–60 (2000).

147. Flood, B. L. & Constance, A. Diabetes Exercise Safety. *Health Care (Don. Mills).* **102,** 47–55 (2002).

148. National Institutes of Health, C. Osteoporosis Prevention, Diagnosis, and Therapy. **17,** 1–29 (2000).

149. WHO Study Group. *Osteoporosis, Assessment of fracture risk and its application to screening for postmenopausal*. (1994). http://apps.who.int/iris/bitstream/10665/39142/1/WHO_TRS_843_eng.pdf

150. BC Medical Association. *Osteoporosis : Diagnosis, Treatment and Fracture Prevention*. *BC Ministry of Health* (2012). http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/osteoporosis

151. Shetty, M., Kumar, M. A. & Prabhu, J. Assessment of Fracture Risk in Osteoporosis. **23,** 101–102 (2010).

152. Fazil, M., Baboota, S., Sahni, J. K., Ameeduzzafar & Ali, J. Bisphosphonates: therapeutics potential and recent advances in drug delivery. *Drug Deliv.* **22,** 1–9 (2015).

153. Kessenich, C. R. Osteonecrosis of the jaw & osteoporosis therapy. *Nurse Pr.* **35,** 51–53 (2010).

154. Nguyen, N. D., Ahlborg, H. G., Center, J. R., Eisman, J. A. & Nguyen, T. V. Residual Lifetime Risk of Fractures in Women and Men. *J. Bone Miner. Res.* **22,** 781–788 (2007).

155. Budlovsky, J. & Dian, L. Questions in osteoporosis management. *B. C. Med. J.* **59,** 106–111 (2017).

156. Drake, M. T., Clarke, B. L. & Khosla, S. Bisphosphonates: Mechanism of action and role in clinical practice. *Mayo Clin. Proc.* **83,** 1–18 (2008).

157. Papaioannou, A. *et al.* 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: Summary. *Cmaj* **182,** 1864–1873 (2010).

158. Khosla, S. *et al.* Benefits and risks of bisphosphonate therapy for osteoporosis. *J. Clin. Endocrinol. Metab.* **97,** 2272–2282 (2012).

159. Arthritis Research UK. *The evidence base for risks and benefits of long term osteoporosis medication in post-menopausal women*. (2015).

160. Osteoporosis Canada. *Drug Treatments*. (2011). www.osteoporosis.ca/multimedia/pdf/publications/Drug_Treatments_EN.pdf

161. Khajuria, D. K., Razdan, R. & Mahapatra, D. R. Drugs for the management of osteoporosis: A review. *Rev. Bras. Reumatol.* **51,** 365–382 (2011).

162. Fleisch, H. Bisphosphonates: mechanisms of action. *Endocr. Rev.* **19,** 80–100 (1998).

163. Cummings, S. & Martin, J. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *... Engl. J. ...* (2009).

164. Diab, D. L. & Watts, N. B. Denosumab in osteoporosis. *Expert Opin. Drug Saf.* **13,** 247–53 (2014).

165. Kostenuik, P. J. *et al.* Denosumab, a Fully Human Monoclonal Antibody to RANKL, Inhibits Bone Resorption and Increases BMD in Knock-In Mice That Express Chimeric (Murine/Human) RANKL*. *J. Bone Miner. Res.* **24,** 182–195 (2009).

166. Amgen Inc. *Risk evaluation and mitigation strategy (REMS): Prolia (denosumab)*. (2010).

167. Musa, M. A., Khan, M. O. F. & Cooperwood, J. S. Medicinal chemistry and emerging strategies applied to the development of selective estrogen receptor modulators (SERMs). *Curr. Med. Chem.* **14,** 1249 (2007).

168. Taranta, A. *et al.* The selective estrogen receptor modulator raloxifene regulates osteoclast and osteoblast activity in vitro. *Bone* **30,** 368–376 (2002).

169. Dutertre, M. & Smith, C. L. Molecular mechanisms of selective estrogen receptor modulator (SERM) action. *J. Pharmacol. Exp. Ther.* **295,** 431–7 (2000).

170. Riggs, B. L. & Hartmann, L. C. 030213 Selective Estrogen-Receptor Modulators — Mechanisms of Action. *N. Engl. J. Med.* **348,** 618–630 (2003).

171. Ettinger, B. *et al.* Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *Jama* **282,** 637–645 (1999).

172. Miller, P. D. *et al.* Effects of Bazedoxifene on BMD and Bone Turnover in Postmenopausal Women: 2-Yr Results of a Randomized, Double-Blind, Placebo-, and Active-Controlled Study. *J. Bone Miner. Res.* **23,** 525–535 (2007).

173. Brixen, K. T., Christensen, P. M., Ejersted, C. & Langdahl, B. L. Teriparatide (biosynthetic human parathyroid hormone 1-34): A new paradigm in the treatment of osteoporosis. *Basic Clin. Pharmacol. Toxicol.* **94,** 260–270 (2004).

174. Grover, H., Luthra, S. & Maroo, S. Teriparatide: A novel means to ultimately achieve true regeneration!!! *J. Clin. Diagnostic Res.* **7,** 1820–1823 (2013).

175. Han, S. L. & Wan, S. L. Effect of teriparatide on bone mineral density and fracture in postmenopausal osteoporosis: Meta-analysis of randomised controlled trials. *Int. J. Clin. Pract.* **66,** 199–209 (2012).

176. Fadda, V., Maratea, D., Trippoli, S. & Messori, A. Gastrointestinal and renal side effects of bisphosphonates: Differentiating between no proof of difference and proof of no difference. *J. Endocrinol. Invest.* **38,** 189–192 (2015).

177. Bamias, A. *et al.* Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors. *J. Clin. Oncol.* **23,** 8580–8587 (2005).

178. Zavras, A. I. & Shanmugham, J. R. Bisphosphonates, Osteoporosis, and Osteonecrosis of the Jaw: A Critical Review of a Large Nested Case???Control Study. *J. Evid. Based. Dent. Pract.* **16,** 136–138 (2016).

179. Otto, S. *et al.* Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: Not just a sporadic coincidence - A multi-centre study. *J. Cranio-Maxillofacial Surg.* **39,** 272–277 (2011).

180. Powell, D. *et al.* Incidence of serious side effects with intravenous bisphosphonate: A clinical audit. *Qjm* **105,** 965–971 (2012).

181. Capeci, C. M. & Tejwani, N. C. Bilateral Low-Energy Simultaneous or Sequential Femoral Fractures in Patients on Long-Term Alendronate Therapy. *J. Bone Jt. Surg.* **91,** 2556–2561 (2009).

182. Odvina, C. V. *et al.* Severely suppressed bone turnover: A potential complication of alendronate therapy. *J. Clin. Endocrinol. Metab.* **90,** 1294–1301 (2005).

183. Abrahamsen, B., Eiken, P. & Eastell, R. Subtrochanteric and Diaphyseal Femur Fractures in Patients Treated With Alendronate: A Register-Based National Cohort Study. *J. Bone Miner. Res.* **24,** 1095–1102 (2009).

184. Clout, A., Narayanasamy, N. & Harris, I. Trends in the incidence of atypical femoral fractures and bisphosphonate therapy. *J. Orthop. Surg.* **24,** 36–40 (2016).

185. Adler, R. A. Bisphosphonates and atypical femoral fractures. *J. Nurse Pract.* **11,** 389–396 (2015).

186. Watts, N. B. *et al.* Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: Coincidence or causal association? *Osteoporos. Int.* **23,** 327–337 (2012).

187. Rizzoli, R. *et al.* Adverse Reactions and Drug–Drug Interactions in the Management of Women with Postmenopausal Osteoporosis. *Calcif. Tissue Int.* **89,** 91–104 (2011).

188. Silverman, S. L. *et al.* Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: Results of a 5-year, randomized, placebo-controlled study. *Osteoporos. Int.* **23,** 351–363 (2012).

189. Clemett, D. & Spencer, C. M. Raloxifene: a review of its use in postmenopausal osteoporosis. *Drugs* **60,** 379–411 (2000).

190. Silverman, S. L. *et al.* Efficacy of Bazedoxifene in Reducing New Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis: Results From a 3-Year, Randomized, Placebo-, and Active-Controlled Clinical Trial*. *J. Bone Miner. Res.* **23,** 1923–1934 (2008).

191. Orwoll, E. S. *et al.* The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J. Bone Miner. Res.* **18,** 9–17 (2003).

192. Klein-Nulend, J., Bacabac, R. G. & Bakker, A. D. Mechanical loading and how it affects bone cells: The role of the osteocyte cytoskeleton in maintaining our skeleton. *Eur. Cells Mater.* **24,** 278–291 (2012).

193. Heaney, R. P. *et al.* Bone dimensional change with age: Interactions of genetic, hormonal, and body size variables. *Osteoporos. Int.* **7,** 426–431 (1997).

194. Ocarino, N. de M. & Serakides, R. Effect of the physical activity on normal bone and on the osteoporosis prevention and treatment. **12,** 149–152 (2006).

195. Ohlsson, C. *et al.* Older men with low serum IGF-1 have an increased risk of incident fractures: The MrOS Sweden study. *J. Bone Miner. Res.* **26,** 865–872 (2011).

196. Chestnut, C. H. Bone Mass and Exercise. *Am. J. Med.* **95,** (1993).

197. Wallace, B. A. & Cumming, R. G. Systematic Review of Randomized Trials of the Effect of Exercise on Bone Mass in Pre- and Postmenopausal Women. *Calcif. Tissue Int.* **67,** 10–18 (2000).

198. Iwamoto, J., Takeda, T. & Ichimura, S. Effect of exercise training and detraining on bone mineral density in postmenopausal women with osteoporosis. *J. Orthop. Sci.* **6,** 128–32 (2001).

199. Brown, J. P. & Josse, R. G. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* **167,** s1–s34 (2002).

200. Ettinger, W. H. *et al.* A Randomized Trial Comparing Aerobic Exercise and Resistance Exercise With a Health Education Program in Older Adults With Knee Osteoarthritis. (2014).

201. International Osteoporosis Foundation. Exercise Recommendations. (2017). https://www.iofbonehealth.org/exercise-recommendations

202. Krege, J. H. *et al.* Fracture risk prediction: importance of age, BMD and spine fracture status. *Bonekey Rep.* **2,** 1–7 (2013).

203. De Laet, C. *et al.* Body mass index as a predictor of fracture risk: A meta-analysis. *Osteoporos. Int.* **16,** 1330–1338 (2005).

204. Telford, R. D. *et al.* Sensitivity of blood lipids to changes in adiposity, exercise, and diet in children. *Med. Sci. Sports Exerc.* **47,** 974–982 (2015).

205. Tremblay, A. *et al.* Effect of intensity of physical activity on body fatness and fat distribution. *Am. J. Clin. Nutr.* **51,** 153–7 (1990).

206. Raeissadat, S. A., Sedighipour, L., Pournajaf, S., Vahab Kashani, R. & Sadeghi, S. Effect of posture training with weighted kypho-orthosis (WKO) on improving balance in women with osteoporosis. *J. Aging Res.* **2014,** (2014).

207. Barnett, A., Smith, B., Lord, S. R., Williams, M. & Baumand, A. Community based group exercise improves balance and reduces falls in at risk older people: A randomised controlled trial. *Age Ageing* **32,** 407–414 (2003).

208. Tomita, M. R., Saharin, S., Rajendran, S., Nochajski, S. M. & Schweitzer, J. A. Psychometrics of the home safety self-assessment tool (HSSAT) to prevent falls in community-dwelling older adults. *Am. J. Occup. Ther.* **68,** 711–718 (2014).

209. Otero, M., Esain, I., Gonzalez-Suarez, A. M. & Gil, S. M. The effectiveness of a basic exercise intervention to improve strength and balance in women with osteoporosis. *Clin. Interv. Aging* **12,** 505–513 (2017).

210. El-Khoury, F., Cassou, B., Charles, M.-A. & Dargent-Molina, P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials Fabienne El-Khoury PhD candidate in epidemiology. **347,** (2017).

211. Resnick, B. *et al.* The impact of osteoporosis, falls, fear of falling and efficacy expectations on exercise among community dwelling older adults. *Orthop. Nurs.* **23,** 1–7 (2008).

212. Chilibeck, P. D., Vatanprasat, H., Cornish, S. M., Abeysekara, S. & Charlesworth, S. Evidence-based risk assessment and recommendations for physical activity: arthritis, osteoporosis, and low back pain. *Appl. Physiol. Nutr. Metab.* **36,** S49–S79 (2011).

213. Pearson, C., Janz, T. & Ali, J. Mental and substance use disorders in Canada. *Stat. Canada* 1–8 (2013). doi:82-624-X

214. The National Institute for Health and Care Excellence. *The NICE Guideline on the Treatment and Depression the Treatment and Management of Depression*. *NICE guidelines [CG90]* (2009).

215. Nemeroff CB & Vale WW. The neurobiology of depression: inroads to treatment and new drug discovery. [Review] [83 refs]. *Ovid Medlin. Clin. Psychiatry* **30322,** 5–13 (2005).

216. Lohoff, F. W. The genetics of major depressive disorder. *Curr. Psychiatry Rep.* **12,** 539–546 (2010).

217. Gerber, P. D. *et al.* The relationship of presenting physical complaints to depressive symptoms in primary care patients. *J. Gen. Intern. Med.* **7,** 170–173 (1992).

218. Cassano, P. & Fava, M. Depression and public health: An overview. *J. Psychosom. Res.* **53,** 849–857 (2002).

219. Moussavi, S. *et al.* Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* **370,** 851–858 (2007).

220. OECD. Pharmaceutical consumption. in *Health at a Glance 2013: OECD Indicators* 102–

103 (OECD Publishing, 2013).

221. Ferrari, A. J. *et al.* Burden of depressive disorder by country, sex, age, and year: findings from the global burden of disease study 2010. *PLos Med* **10,** e1001547 (2013).

222. Zhong, W. *et al.* Time trends of antidepressant drug prescriptions in men versus women in a geographically defined US population. *Arch. Womens. Ment. Health* **17,** 485–492 (2014).

223. Vaswani, M., Linda, F. K. & Ramesh, S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry* **27,** 85–102 (2003).

224. Lambert, O. & Bourin, M. SNRIs: mechanism of action and clinical features. *Expert Rev. Neurother.* **2,** 846–858 (2002).

225. Medco. America's state of mind. 1–11 (2011). http://apps.who.int/medicinedocs/documents/s19032en/s19032en.pdf

226. Santarsieri, D. & Schwartz, T. L. Antidepressant efficacy and side-effect burden: A quick guide for clinicians. *Drugs Context* **4,** 1–12 (2015).

227. Thase, M. E. Are SNRIs more effective than SSRIs? A review of the current state of the controversy. *Psychopharmacol. Bull.* **41,** 58–85 (2008).

228. Nutt, D. J. *et al.* Mechanisms of action of selective serotonin reuptake inhibitors in the treatment of psychiatric disorders. *Eur. Neuropsychopharmacol.* **9 Suppl 3,** S81–S86 (1999).

229. Jakobsen, J. C. *et al.* Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry* **17,** 58 (2017).

230. Cipriani, A. *et al.* Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* **373,** 746–758 (2009).

231. Undurraga, J. & Baldessarini, R. J. Randomized, Placebo-Controlled Trials of Antidepressants for Acute Major Depression: Thirty-Year Meta-Analytic Review. *Neuropsychopharmacology* **37,** 851–864 (2012).

232. Fournier, J. C. *et al.* Antidepressant Drug effects and Depression Severity: A Patient-Level Meta-Analysis. *JAMA* **303,** 47–53 (2010).

233. Gibbons, R. D., Hur, K., Brown, C. H., Davis, J. M. & Mann, J. J. Who benefits from antidepressants? *Arch. Gen. Psychiatry* **69,** 572–579 (2012).

234. Thorlund, K. *et al.* Comparative efficacy and safety of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in older adults: A network meta-analysis. *J. Am. Geriatr. Soc.* **63,** 1002–1009 (2015).

235. Fabre, L., Birkhimer, L. J., Zaborny, B. A., Wong, L. F. & Kapik, B. . Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. *Int. Clin. Psychopharmacol.* **11,** 119–127 (1996).

236. Burke, W. J., Gergel, I., Bose, A. & Ph, D. Fixed-dose trial of the single isomer SSRI escitalopram in Depressed Outpatients. *J. Clin. Psychiatry* **63,** 331–336 (2002).

237. Papakostas, G. I., Thase, M. E., Fava, M., Nelson, J. C. & Shelton, R. C. Are Antidepressant Drugs That Combine Serotonergic and Noradrenergic Mechanisms of Action More Effective Than the Selective Serotonin Reuptake Inhibitors in Treating Major Depressive Disorder? A Meta-analysis of Studies of Newer Agents. *Biol. Psychiatry* **62,** 1217–1227 (2007).

238. de Silva, V. A. & Hanwella, R. Efficacy and tolerability of venlafaxine versus specific serotonin reuptake inhibitors in treatment of major depressive disorder. *Int. Clin. Psychopharmacol.* **27,** 8–16 (2012).

239. Papakostas, G. I. & Fava, M. A meta-analysis of clinical trials comparing milnacipran, a serotonin-norepinephrine reuptake inhibitor, with a selective serotonin reuptake inhibitor for the treatment of major depressive disorder. *Eur. Neuropsychopharmacol.* **17,** 32–36 (2007).

240. Machado, M. & Einarson, T. R. Comparison of SSRIs and SNRIs in major depressive disorder: A meta-analysis of head-to-head randomized clinical trials. *J. Clin. Pharm. Ther.* **35,** 177–188 (2010).

241. Nemeroff, C. B. *et al.* Comprehensive Analysis of Remission (COMPARE) with Venlafaxine versus SSRIs. *Biol. Psychiatry* **63,** 424–434 (2008).

242. Stahl, S. M. *et al.* A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. *Prim. Care Companion J. Clin. Psychiatry* **6,** 159–166 (2004).

243. Golden, R. N., Rudorfer, M. V, Sherer, M. A., Linnoila, M. & Potter, W. Z. Bupropion in Depression. *Arch. Gen. Psychiatry* **45,** 139–143 (1988).

244. Zung. Comparative Efficacy and Safety of Bupropion and Placebo in the Treatment of Depression. 83–91 (1983).

245. Lineberry, C. G. *et al.* A fixed-dose (300mg) efficacy study of bupropion and placebo in depression outpatients. *Clin. Psychiatry* **51,** 194–9 (1999).

246. Maneeton, B., Maneeton, N., Eurviriyanukul & Srisurapanont, M. Efficacy, tolerability, and acceptability of bupropion for major depressive disorder: a meta-analysis of randomized–controlled trials comparison with venlafaxine. *Drug Des. Devel. Ther.* **7,** 1053 (2013).

247. ConsumerReports. Best Buy Drugs: Using Antidepressant to Treat Depression. *Consum. Union U.S., Inc.* 1–30 (2013).

248. Hieronymus, F., Emilsson, J. F., Nilsson, S. & Eriksson, E. Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression. *Mol. Psychiatry* **21,** 523–530 (2016).

249. Papakostas, G. I., Nelson, J. C., Kasper, S. & Möller, H.-J. A meta-analysis of clinical trials comparing reboxetine, a norepinephrine reuptake inhibitor, with selective serotonin

reuptake inhibitors for the treatment of major depressive disorder. *Eur. Neuropsychopharmacol.* **18,** 122–127 (2008).

250. Lanteigne, A. *et al.* Serotonin–Norepinephrine Reuptake Inhibitor and Selective Serotonin Reuptake Inhibitor Use and Risk of Fractures: A New-User Cohort Study Among US Adults Aged 50 Years and Older. *CNS Drugs* **29,** 245–252 (2015).

251. Coupland, C. A. C. *et al.* A study of the safety and harms of antidepressant drugs for older people: A cohort study using a large primary care database. *Health Technol. Assess. (Rockv).* **15,** 5–218 (2011).

252. Dudley, M., Goldney, R. & Hadzi-Pavlovic, D. Are adolescents dying by suicide taking SSRI antidepressants? A review of observational studies. *Australas. Psychiatry* **18,** 242–245 (2010).

253. Gibbons, R. D., D, P., Hur, K., Bhaumik, D. K. & Mann, J. J. Rates and Rate of Early Adolescent Suicide. *Psychiatry Interpers. Biol. Process.* 1898–1904 (2006). doi:10.1176/ajp.2006.163.11.1898

254. Libby, A. M. *et al.* Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *Am. J. Psychiatry* **164,** 884–891 (2007).

255. Isacsson, G. & Ahlner, J. Antidepressants and the risk of suicide in young persons - prescription trends and toxicological analyses. *Acta Psychiatr. Scand.* **129,** 296–302 (2014).

256. Gibbons, R. D. *et al.* Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am. J. Psychiatry* **164,** 1356–1363 (2007).

257. Barbui, C., Esposito, E. & Cipriani, A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. *CMAJ* **180,** 291–7 (2009).

258. Tiihonen, J. *et al.* Antidepressants and the Risk of Suicide, Attempted Suicide, and Overall Mortality in a Nationwide Cohort. *Arch. Gen. Psychiatry* **63,** (2006).

259. Søndergård, L., Kvist, K., Andersen, P. K. & Kessing, L. V. Do antidepressants precipitate youth suicide? A nationwide pharmacoepidemiological study. *Eur. Child Adolesc. Psychiatry* **15,** 232–240 (2006).

260. Hewett, K. *et al.* Double-blind, placebo-controlled comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. *J. Psychopharmacol.* **24,** 1209–1216 (2010).

261. Doellinger, O. von *et al.* Spontaneous seizures after ECT in a patient medicated with bupropion, sertraline and risperidone. *Trends Psychiatry Psychother.* **38,** 111–113 (2016).

262. Fava, M. *et al.* 5 Years of Clinical Experience With Bupropion HCl: From Bupropion to Bupropion SR to Bupropion XL. *J Clin PsychiatryPrim Care Companion J Clin Psychiatry* **77,** 106–113 (2005).

263. Sartori, C. R. *et al.* The antidepressive effect of the physical exercise correlates with

increased levels of mature BDNF, and proBDNF proteolytic cleavage-related genes, p11 and tPA. *Neuroscience* **180,** 9–18 (2011).

264. Rethorst, C. D., Wipfli, B. M. & Landers, D. M. The antidepressive effects of exercise: A meta-analysis of reandomized trials. *Sport. Med.* **39,** 491–511 (2009).

265. Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G. & Chambliss, H. O. Exercise treatment for depression: Efficacy and dose response. *Am. J. Prev. Med.* **28,** 1–8 (2005).

266. Blumenthal, J. A. *et al.* Exercise and Pharmacotherapy in the Treatment of Major Depressive Disorder. *Psychosom. Med.* **69,** 587–596 (2007).

267. Carneiro, L. S. F., Fonseca, A. M., Vieira-Coelho, M. A., Mota, M. P. & Vasconcelos-Raposo, J. Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: A randomized clinical trial. *J. Psychiatr. Res.* **71,** 48–55 (2015).

268. Mota-Pereira, J. *et al.* Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. *J. Psychiatr. Res.* **45,** 1005–1011 (2011).

269. Trivedi, M. H. *et al.* Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. *J. Clin. Psychiatry* **72,** 677–84 (2011).

270. Blumenthal, J. Effects of exercise training on older patients with major depression. *Arch.* **159,** (1999).

271. Dimeo, F., Bauer, M. & Varahram, I. Benefits from aerobic exercise in patients with major depression: a pilot study. *Br. J. Sport. …* **35,** 114–7 (2001).

272. Papakostas, G. I. *et al.* Quality of life assessments in major depressive disorder: A review of the literature. *Gen. Hosp. Psychiatry* **26,** 13–17 (2004).

273. Schuch, F. B. *et al.* Exercise improves physical and psychological quality of life in people with depression: A meta-analysis including the evaluation of control group response. *Psychiatry Res.* **241,** 47–54 (2016).

274. Ishak, W. W. *et al.* Quality of life in patients suffering from insomnia. *Innov. Clin. Neurosci.* **9,** 13–26 (2012).

275. Lawlor, D. A. & Hopker, S. W. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *BMJ* **322,** 763–7 (2001).

276. Craft, L. L. & Perna, F. M. The Benefits of Exercise for the Clinically Depressed. *Prim. Care Companion J. Clin. Psychiatry* **6,** 104–111 (2004).

277. Brosse, A. L., Sheets, E. S., Lett, H. S. & Blumenthal, J. A. Exercise and the Treatment of Clinical Depression in Adults Recent Findings and Future Directions. *Sport. Medicat.* **32,** 741–760 (2002).

278. Cooney, G. M. *et al.* Exercise for depression (review). *Cochrane Libr.* (2013). doi:10.1002/14651858.CD004366.pub6.www.cochranelibrary.com

279. North, T. C., McCullagh, P. & Tran, Z. U. Effect of Exercise on Depression. *Exerc. Sport Sci. Rev.* **18,** 379 (1990).

280. Craft, L. L. & Landers, D. M. The effect of exercise on clinical depression and depression resulting from mental illness: a meta-analysis. *J. Sport Exerc. Psychol.* **20,** 339–357 (1998).

281. Deslandes, A. *et al.* Exercise and mental health: Many reasons to move. *Neuropsychobiology* **59,** 191–198 (2009).

282. Eyre, H. & Baune, B. T. Neuroimmunological effects of physical exercise in depression. *Brain. Behav. Immun.* **26,** 251–266 (2012).

283. Stathopoulou, G., Powers, M. B., Berry, A. C., Smits, J. a J. & Otto, M. W. Exercise Interventions for Mental Health: A Quantitative and Qualitative Review. *Clin Psychol Sci Pr.* **13,** 179–193 (2006).

284. DeVries, H. A. Tension reduction with exercise. in *Exercise and Mental Health* 99–104 (Hemisphere Publishing Corp, 1987).

285. Rethorst, C. D. *et al.* Pro-Inflammatory Cytokines as Predictors of Antidepressant Effects of Exercise inMajor Depressive Disorder. **18,** 1119–1124 (2013).

286. Helmich, I. *et al.* Neurobiological alterations induced by exercise and their impact on depressive disorders [corrected]. *Clin. Pract. Epidemiol. Ment. Health* **6,** 115–25 (2010).

287. Schuch, F. B. arreto *et al.* The effects of exercise on oxidative stress (TBARS) and BDNF in severely depressed inpatients. *Eur. Arch. Psychiatry Clin. Neurosci.* **264,** 605–613 (2014).

288. Lin, T.-W. & Kuo, Y.-M. Exercise Benefits Brain Function: The Monoamine Connection. *Brain Sci.* **3,** 39–53 (2013).

289. Heyes, M. P., Garnett, E. S. & Coates, G. Nigrostriatal dopaminergic activity is increased during exhaustive exercise stress in rats. *Life Sci.* **42,** 1537–1542 (1988).

290. de Castro, J. M. & Duncan, G. Operantly conditioned running: effects on brain catecholamine concentrations and receptor densities in the rat. *Pharmacol. Biochem. Behav.* **23,** 495–500 (1985).

291. Carneiro, L. S. F. *et al.* Monoamines and cortisol as potential mediators of the relationship between exercise and depressive symptoms. *Eur. Arch. Psychiatry Clin. Neurosci.* **267,** 117–121 (2017).

292. Ranjbar, E. *et al.* Depression and Exercise: A Clinical Review and Management Guideline. *Asian J. Sports Med.* **6,** 0–5 (2015).

293. Sims, J. *et al.* Family caregivers of people with dementia. *Int. J. Geriatr. Psychiatry* **24,** 76–83 (2009).

294. Knubben, K. *et al.* A randomised, controlled study on the effects of a short-term endurance training programme in patients with major depression * Commentary. *Br. J. Sports Med.* **41,** 29–33 (2006).

295. Penninx, B. W. J. H. *et al.* Exercise and depressive symptoms: A comparison of aerobic and resistance exercise effects on emotional and physical function in older persons with high and low depressive symptomatology. *J. Gerontol. Psychol. Sci.* **57B,** 124–132 (2002).

296. Tremblay, M. S. *et al.* New Canadian physical activity guidelines. *Appl. Physiol. Nutr. Metab.* **36,** 36–58 (2011).

297. Exercise is Medicine. *Exercising with Anxiety and Depression*. (2013). http://www.exerciseismedicine.org/support_page.php/your-rx-for-health-series/

298. Kim, Y. S. *et al.* Relationship between physical activity and general mental health. *Prev. Med. (Baltim).* **55,** 458–463 (2012).

299. Makki, J. Diversity of breast carcinoma: Histological subtypes and clinical relevance. *Clin. Med. Insights Pathol.* **8,** 23–31 (2015).

300. Canadian Canacer Society's Advisory Committee on Cancer Statistics. *Canadian Cancer Statistics 2017*. *Canadian Cancer Society* (2017). doi:0835-2976

301. American Cancer Society. *Breast cancer facts & figures*. *American Cancer Society Inc.* (2015). doi:10.1016/B978-1-4377-1757-0.00028-7

302. Miller, K. D. *et al.* Cancer treatment and survivorship statistics, 2016. *CA. Cancer J. Clin.* **66,** 271–289 (2016).

303. Chen, K. *et al.* Comparative effectiveness study of breast-conserving surgery and mastectomy in the general population: A NCDB analysis. *Oncotarget* **6,** 40127–40 (2015).

304. Eriksson, D. & Stigbrand, T. Radiation-induced cell death mechanisms. *Tumor Biol.* **31,** 363–372 (2010).

305. EBCTCG. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801. *Lancet* **378,** 771–784 (2011).

306. Smith, B. D. *et al.* Effectiveness of radiation therapy for older women with early breast cancer. *J. Natl. Cancer Inst.* **98,** 681–690 (2006).

307. Posner, J. B. Side effects of radiation therapy. *Neurol. Complicat. cancer* 311–337 (1995).

308. Kaklamani, V. G. & Gradishar, W. J. Epirubicin Versus Doxorubicin: Which Is the Anthracycline of Choice for the Treatment of Breast Cancer? *Clin. Breast Cancer* **4,** S26–S33 (2003).

309. Szuławska, A. & Czyz, M. Molecular mechanisms of anthracyclines action. *Postepy Hig. Med. Dosw. (Online)* **60,** 78–100 (2006).

310. EBCTCG. Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *Lancet* **379,** 132–44 (2012).

311. Chang, M. Tamoxifen resistance in breast cancer. *Biomol. Ther. (Seoul).* **20,** 256–67

(2012).

312. Fisher, B. *et al.* B24-Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* **353,** 1993–2000 (1999).

313. BIG Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N. Engl. J. Med.* **353,** 1095–1104 (2005).

314. Coombes, R. *et al.* Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* **369,** 559–570 (2007).

315. Howell, P. A. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* **365,** 60–62 (2005).

316. Hayes, E. L. & Lewis-Wambi, J. S. Mechanisms of endocrine resistance in breast cancer: an overview of the proposed roles of noncoding RNA. *Breast Cancer Res.* **17,** 40 (2015).

317. EBCTCG. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. *Lancet* **378,** 771–784 (2011).

318. Dowsett, M. *et al.* Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J. Clin. Oncol.* **28,** 509–518 (2010).

319. Curigliano, G. *et al.* Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. *Ann. Oncol.* **23,** (2012).

320. Cobleigh, M. A. *et al.* Multinational study of efficacy and the safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastic disease. *J. Clin. Oncol.* **17,** 2639 (1999).

321. Valachis, A., Nilsson, C. & Press, D. Cardiac risk in the treatment of breast cancer: assessment and management. *Breast cancer (Dove Med. Press.* **7,** 21–35 (2015).

322. Nahta, R., Yu, D., Hung, M.-C., Hortobagyi, G. N. & Esteva, F. J. Mechanisms of Disease: understanding resistance to HER2-targeted therapy in human breast cancer. *Nat. Clin. Pract. Oncol.* **3,** 269–280 (2006).

323. Romond, E. H. *et al.* Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. *N. Engl. J. Med.* **353,** 1673–1684 (2005).

324. Maher, M. Current and Emerging Treatment Regimens for HER2-Positive Breast Cancer. *P T* **39,** 206–12 (2014).

325. Toi, M. *et al.* Lapatinib monotherapy in patients with relapsed, advanced, or metastatic breast cancer: efficacy, safety, and biomarker results from Japanese patients phase II studies. *Br. J. Cancer* **101,** 1676–1682 (2009).

326. Verma, S. *et al.* Trastuzumab emtansine for HER2-positive advanced breast cancer. *New*

*Eng* **367,** 1783–1791 (2012).

327. Gärtner, R. *et al.* Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA* **302,** 1985–1992 (2009).

328. Vilholm, O. J., Cold, S., Rasmussen, L. & Sindrup, S. H. The postmastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. *Br. J. Cancer* **99,** 604–610 (2008).

329. Steegers, M. A., Wolters, B., Evers, A. W., Strobbe, L. & Wilder-Smith, O. H. Effect of Axillary Lymph Node Dissection on Prevalence and Intensity of Chronic and Phantom Pain After Breast Cancer Surgery. *J. Pain* **9,** 813–822 (2008).

330. Runowicz, C. D. *et al.* American Cancer Society / American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *A Cancer J. Clin.* **66,** 43–73 (2015).

331. Pinto, A. C. & De Azambuja, E. Improving quality of life after breast cancer: Dealing with symptoms. *Maturitas* **70,** 343–348 (2011).

332. Ahmed, R. L., Prizment, A., Lazovich, D., Schmitz, K. H. & Folsom, A. R. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. *J. Clin. Oncol.* **26,** 5689–96 (2008).

333. Cormier, J. N. *et al.* Minimal limb volume change has a significant impact on breast cancer survivors. *Lymphology* **42,** 161–175 (2009).

334. DiSipio, T., Rye, S., Newman, B. & Hayes, S. Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. *Lancet Oncol.* **14,** 500–515 (2013).

335. Elumelu-Kupoluyi, T. N., Adenipekun, A. A. & Ntekim, A. I. Pain associated with secondary lymphedema among cancer patients. *J. Palliat. Care* **29,** 253–257 (2013).

336. Lawenda, B. D., Mondry, T. E. & Johnstone, P. A. S. Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. *A Cancer J. Clin. J. Clin.* **59,** 8–24 (2009).

337. Whelan, T. J., Levine, M., Julian, J., Kirkbride, P. & Skingley, P. The effects of radiation therapy on quality of life of women with breast carcinoma: results of a randomized trial. Ontario Clinical Oncology Group. *Cancer* **88,** 2260–2266 (2000).

338. Hau, E. *et al.* The impact of breast cosmetic and functional outcomes on quality of life: Long-term results from the St. George and Wollongong randomized breast boost trial. *Breast Cancer Res. Treat.* **139,** 115–123 (2013).

339. Chen, M.-F. *et al.* Predictive factors of radiation-induced skin toxicity in breast cancer patients. *BMC Cancer* **10,** 508 (2010).

340. Jacob, S. *et al.* Early detection and prediction of cardiotoxicity after radiation therapy for breast cancer: the BACCARAT prospective cohort study. *Radiat. Oncol.* **11,** 54 (2016).

341. Darby, S. C., McGale, P., Taylor, C. W. & Peto, R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort

study of about 300 000 women in US SEER cancer registries. *Lancet Oncol.* **6,** 557–565 (2005).

342. Matzinger, O. *et al.* Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925). *Acta Oncol. (Madr).* **49,** 24–34 (2010).

343. EBCTCG. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet* **366,** 2087–2106 (2005).

344. Roychoudhuri, R. *et al.* Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study. *BMC Cancer* **7,** 9 (2007).

345. Taylor, C. W. & Kirby, A. M. Cardiac Side-effects From Breast Cancer Radiotherapy. *Clin. Oncol.* **27,** 621–629 (2015).

346. Sjövall, K., Strömbeck, G., Löfgren, A., Bendahl, P.-O. & Gunnars, B. Adjuvant radiotherapy of women with breast cancer – Information, support and side-effects. *Eur. J. Oncol. Nurs.* **14,** 147–153 (2010).

347. Singla, P. K. & Iliskovic, N. Doxorubicin-induced cardiomyopathy. *N. Engl. J. Med.* **339,** 900–905 (1998).

348. Geisberg, C. A. & Sawyer, D. B. Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage. *Curr. Hypertens. Rep.* **12,** 404–410 (2010).

349. Yu, A. F. & Jones, L. W. Breast cancer treatment-associated cardiovascular toxicity and effects of exercise countermeasures. *Cardio-Oncology* **2,** 1 (2016).

350. Swain, S. M., Whaley, F. S. & Ewer, M. S. Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials. *Cancer* **97,** 2869–2879 (2003).

351. Du, X. L., Osborne, C. & Goodwin, J. Population-based assessment for hospitalizations for toxicity from chemotherapy in older women with breast cancer. *J. Clin. Oncol.* **20,** 4636–4642 (2002).

352. Hassett, M. J., O'Malley, A. J., Pakes, J. R., Newhouse, J. P. & Earle, C. C. Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer. *J. Natl. Cancer Inst.* **98,** 1108–1117 (2006).

353. Lorizio, W. *et al.* Clinical and biomarker predictors of side effects from tamoxifen. *Breast Cancer Res. Treat.* **132,** 1107–1118 (2012).

354. Wise, J. Menopausal symptoms may be confused with side effects of tamoxifen. *Bmj* **6649,** i6649 (2016).

355. Conte, P. & Frassoldati, a. Aromatase inhibitors in the adjuvant treatment of postmenopausal women with early breast cancer: Putting safety issues into perspective. *Breast J* **13,** 28–35 (2007).

356. Budzar, A. U. Clinical features of joint symptoms observed in the 'Arimidex', tamoxifen, alone or in combination (ATAC) trial. *J. Clin. Oncol.* **24,** 551 (2006).

357. Cuppone, F. *et al.* Do adjuvant aromatase inhibitors increase the cardiovascular risk in postmenopausal women with early breast cancer? Meta-analysis of randomized trials. *Cancer* **112,** 260–267 (2008).

358. Gamucci, T. *et al.* Optimal tolerability and high efficacy of a modified schedule of lapatinib-capecitabine in advanced breast cancer patients. *J. Cancer Res. Clin. Oncol.* **140,** 221–226 (2014).

359. Conlin, A. K. *et al.* Phase II trial of weekly nanoparticle albumin-bound paclitaxel with carboplatin and trastuzumab as first-line therapy for women with HER2-overexpressing metastatic breast cancer. *Clin. Breast Cancer* **10,** 281–7 (2010).

360. Courneya, K. S. *et al.* Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. *J. Clin. Oncol.* **25,** 4396–4404 (2007).

361. McNeely, M. L. *et al.* Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ* **175,** 34–41 (2006).

362. Speck, R. M., Courneya, K. S., Mâsse, L. C., Duval, S. & Schmitz, K. H. An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. *J. Cancer Surviv.* **4,** 87–100 (2010).

363. EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* **365,** 1687–717 (2005).

364. Heydarnejad, M. S., Hassanpour, D. a & Solati, D. K. Factors affecting quality of life in cancer patients undergoing chemotherapy. *Afr. Health Sci.* **11,** 266–70 (2011).

365. Courneya, K. S. *et al.* Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. *J. Clin. Oncol.* **21,** 1660–1668 (2003).

366. Fong, D. Y. T. *et al.* Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *Bmj* **344,** e70–e70 (2012).

367. Mejia, S. & Lite, R. S. Breast Cancer and Exercise. *Strength Cond. J.* **32,** 57–59 (2010).

368. Courneya, K. S. *et al.* Effects of exercise dose and type during breast cancer chemotherapy: Multicenter randomized trial. *J. Natl. Cancer Inst.* **105,** 1821–1832 (2013).

369. Rock, C. L. *et al.* Nutrition and Physical Activity Guidelines for Cancer Survivors. *CA. Cancer J. Clin.* **62,** 243–274 (2012).

370. Jones, L. W. *et al.* Rationale and design of the Exercise Intensity Trial (EXCITE): A randomized trial comparing the effects of moderate versus moderate to high-intensity aerobic training in women with operable breast cancer. *BMC Cancer* **10,** 531 (2010).

371. Stefani, L., Galanti, G. & Klika, R. Clinical Implementation of Exercise Guidelines for Cancer Patients: Adaptation of ACSM's Guidelines to the Italian Model. *J. Funct. Morphol. Kinesiol.* **2,** 4 (2017).

372. Exercise is Medicine. *Exercising with Cancer*. (2016). http://www.exerciseismedicine.org/support_page.php/your-rx-for-health-series/

373. Courneya, K. S. *et al.* Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med. Sci. Sports Exerc.* **46,** 1744–1751 (2014).

374. Denysschen, C. A. *et al.* Exercise intervention in breast cancer patients with aromatase inhibitor-associated arthralgia: A pilot study. *Eur. J. Cancer Care (Engl).* **23,** 493–501 (2014).

375. Irwin, M. L. *et al.* Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *J. Clin. Oncol.* **33,** 1104–1111 (2015).

376. Schmitz, K. H. *et al.* American college of sports medicine roundtable on exercise guidelines for cancer survivors. *Med. Sci. Sports Exerc.* **42,** 1409–1426 (2010).

377. Hayes, S. C., Speck, R. M., Reimet, E., Stark, A. & Schmitz, K. H. Does the effect of weight lifting on lymphedema following breast cancer differ by diagnostic method: Results from a randomized controlled trial. *Breast Cancer Res. Treat.* **130,** 227–234 (2011).

378. Schwartz, A. L., Winters-Stone, K. & Gallucci, B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. *Oncol. Nurs. Forum* **34,** 627–633 (2007).

379. Schmitz, K. H. *et al.* Weight Lifting in Women with Breast-Cancer–Related Lymphedema. *N. Engl. J. Med.* **361,** 664–673 (2009).

380. Cormie, P. *et al.* Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: A randomised controlled trial. *J. Cancer Surviv.* **7,** 413–424 (2013).

381. Ligibel, J. A. *et al.* Randomized trial of a physical activity intervention in women with metastatic breast cancer. *Cancer* **122,** 1169–1177 (2016).

382. Drouin, J. Aerobic exercise training effects on physical function, fatigue and mood, immune status, and oxidative stress in subjects undergoing radiation treatment for breast cancer. (Detroit: Wayne State University, 2002).

383. Morey, M. C. *et al.* Effects of Home-based Diet and Exercise on Functional Outcomes Among Older, Overweight Long-Term Cancer Survivors: The RENEW: Randomized Clinical Trial. *JAMA J. Am. Med. Assoc.* **301,** 1883–1891 (2009).

384. Canadian Institute for Health Information. National Health Expenditure Trends , 1975 to 2013. *JAMA* **36,** 423–5 (2013).

385. Kolber, M., Lee, J. & Nickonchuk, T. *Price Comparison of Commonly Prescribed Pharmaceuticals in Alberta*. (2014). https://www.acfp.ca/wp-content/uploads/2016/03/ACFPPricingDoc2016.pdf

386. Ontario Ministry of Health and Long-Term Care. *Exemestane (for early breast cancer)*. (2008). https://www.health.gov.on.ca/en/pro/programs/drugs/ced/pdf/exemestane.pdf